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Section of Anæsthetics

President—BERNARD JOHNSON, F.F.A. R.C.S.

[*February* 4, 1955]

The Physiology of Respiration in Infants and Young Children

By J. E. HALL, M.B., Ch.B.

(*The Hospital for Sick Children, London*)

IN the management of anæsthesia for the adult patient, the respiration is used as an important sign of the level of anæsthesia. In pædiatric practice the interpretation is more difficult owing to the changes in respiration occurring as the child grows. These variations in the anatomical and physiological development of the child's respiratory system form the subject of this paper.

Development of the lung.—The fœtal lung develops by a process of budding and elongation of the primary stem into the mesodermal mass, and after birth this process continues increasing the size of the lungs and the bronchial tree. The progress of this development has been studied by Engel (1947) in a series of examinations of post-mortem material and his results are summarized in Table I. The lung volume enlarges rapidly in

TABLE I

Age	Lung volume c.c.	Surface area sq. cm.	Tracheal length cm.	Tracheal diameter mm.
Birth	100	16,000	4·0	6·0
3/12	150	—	3·8	6·8
6/12	230	57,000	4·2	7·2
12/12	400	—	4·3	7·8
18/12	470	111,000	4·5	8·8
2	500	184,000	5·0	9·5
3	550	236,000	5·3	—
4	600	—	5·4	11·0
5	700	—	5·6	—
6	800	—	5·7	—

the first year and then slows down till after the second year when the growth becomes roughly parallel to the increasing weight of the child. The internal development of the lung is more important and the estimates of the surface area show a higher rate of development, again more marked during the first two years. In contrast the air passages grow slowly and whereas the trachea takes two years to double its volume, the lung volume has reached this stage in twelve months.

The thoracic cage must grow to contain this increasing lung volume and its growth is therefore greatest in the first eighteen months, during which time its circumference increases by 50%. The shape is usually described as round in comparison to the adult chest, but even at birth there is a difference of 2 cm. between the antero-posterior and transverse diameters of the chest. This difference increases slowly at first during childhood, as a result of the different rate of growth in the two diameters, but after the age of 2 years, the ribs, which have been almost horizontal since birth, now start to slope downwards and this contributes to the increasing difference in the chest diameters. The main change in the shape of the chest, however, occurs during puberty when the difference in the two diameters of the chest alters from 6 cm. to 12 cm.

Respiration in the child.—The physiological investigation of respiration in the child has been confined principally to neonates and to school children, as between these ages it is impossible to obtain the co-operation of the subject. The results of Denning and Hienner (1936) and Cross (1949) on neonates agree very well, and their average results suggest 20 ml. as the tidal volume and 30 per minute as the rate. These are the resting values and are considerably exceeded when the child is active but the increase in ventilation demands a high energy expenditure and cannot be maintained for any length of time. When the respiration of school children has been investigated it has usually had a clinical bias to provide a standard for the assessment of the variations produced by disease. As a result

there are a number of observations on such limiting factors as maximum ventilation rate and vital capacity but very few on normal quiet respiration. The results of two recent workers Piechaud (1951) and Ferris (Ferris *et al.*, 1952) are shown in Table II. The considerable difference in the results for vital capacity and the high value for the tidal volume are undoubtedly due to the difficulties of obtaining figures under constant basal conditions and suggested that the investigation of the respiration of children under anæsthesia would be of value.

TABLE II

Age	Piechaud Tidal volume ml.	Piechaud Vital capacity ml.	Ferris Vital capacity ml.
4	300	500	—
5	320	580	1,290
6	360	660	1,650
7	400	820	1,930
8	460	980	2,160
9	500	1,150	2,190
10	560	1,360	2,230
11	600	1,600	2,540
12	680	1,680	3,750
13	796	1,960	3,810

TABLE III

Age	Tidal volume ml.	Rate per minute	Minute volume ml.
6/12	64	55	3,500
12/12	79	45	3,700
18/12	131	33	4,300
2	143	30	4,400
3	156	31	4,900
4	180	30	5,500
5	192	28	5,400
6	199	27	6,000
7	204	30	6,300
8	228	25	6,200

Respiration under anæsthesia.—Such an investigation would reduce the variations due to the non-co-operation of the subject but naturally would add those of premedication and type of anæsthesia. To minimize these a large series of cases were studied and for convenience in the operating theatre the apparatus was kept small and portable. A small Krogh type spirometer was used, writing directly on the drum and connected to the patient by the usual anæsthetic tubing and face mask. The cases studied were principally "cold" operation cases of hernias, squints, and plastic repairs, of the age groups 3 months to 8 years. The measurements were made at the end of the operation just before the patient was returned to the ward. The dead space of this apparatus was large but its effect was minimized by keeping the time of recording short and repeating after a few breaths of air. 487 of the records were analysed and the results are shown in Table III. This shows a rapid increase in the tidal volume during the first two years, which then slows down, similar in pattern to that seen for the volume of the lung in Table I. The rate changes in an inverse manner, starting rapidly and slowing down during the first two years, then remaining steady. These two changes produce a more gradual increase in the minute volume. As the observations were made on children over the age of 3 months the variable pattern of respiration seen by Denning and Hienner (1936) in neonates was not seen and the respiration was always regular but not of adult pattern during the first two years. During this period the respiration is almost entirely abdominal in character as the ribs still maintain their original horizontal position. The thoracic cage can only enlarge slightly by means of the so-called "bucket-handle" movement of the ribs and respiration is maintained principally by diaphragmatic movement. Thus the tidal volume is limited and increased respiratory demands can only be met by an increase in rate. Interference with the free movement of the diaphragm by the presence of gas in the stomach or limitation of the abdominal movement either by surgical manipulations or the use of the prone position will reduce the tidal volume. When the ribs become more oblique after the age of 18 months the thoracic movements are increased for now the ribs can move up and down lifting the sternum and so enlarging the thorax. This allows the tidal volume to be increased to compensate for higher oxygen demands and the increase in rate is only used as a reserve mechanism.

The rapid respiratory rate of the infant under anæsthesia might be explained on the basis of carbon dioxide retention, and attempts were made to estimate the alveolar carbon dioxide in a number of small babies. No satisfactory result was obtained as the method, that of Rahn and Otis (1949), did not function well on their small tidal volumes and rapid respirations. Over the age of 3 the method was satisfactory, but the average alveolar carbon dioxide content was normal or a little below (4·3–4·5%). However, the suggestion that the rapid respirations might be due to carbon dioxide retention is supported by a consideration of the dead space of the child in relation to that of the adult. Anatomically the dead space may be defined as that part of the respiratory tract which does not allow respiratory exchange to take place and consists of the oronasopharynx, trachea, bronchi and bronchioles. At the end of expiration this space is filled with expired air; the next inspiration will draw in fresh air, which will be diluted by this volume of expired air and the resultant mixture reaching the alveoli will contain, therefore, less oxygen but more carbon dioxide than the atmospheric air. As the composition of the atmospheric air is

constant, the concentrations of the gases reaching the alveoli during a given inspiration are in direct relationship to those removed during the previous expiration and therefore sudden changes in the blood gases are avoided. By measuring the concentration of a gas in the inspired, expired and alveolar air, and knowing the tidal volume, it is possible to calculate the volume of the diluting gas, or dead space, which can be defined physiologically as that volume of the inspired air which does not take part in respiratory exchange. Assuming that the adult relationship between the expired and alveolar carbon dioxide content remains true for infants, the dead space can be estimated as one-fifth of the tidal volume (Table IV).

TABLE IV

Age	Tidal volume ml.	Dead space ml.
6/12	64	12
12/12	79	16
18/12	131	26
2	143	29
3	156	31
4	180	36
5	192	38
6	199	40
7	204	42
8	228	46

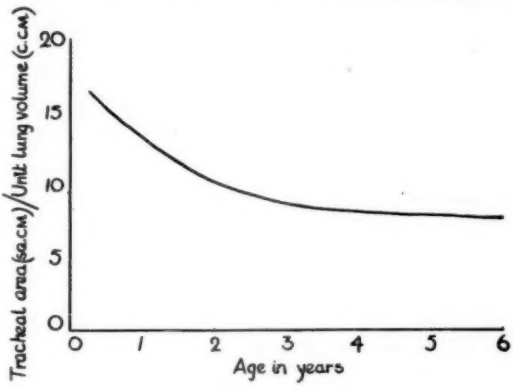

FIG. 1.

These figures indicate the magnitude of the dead space but do not show the relative changes. The cross-sectional area of the trachea is directly proportional to the dead space and this has been divided by the lung volume and plotted against age to obtain the graph, Fig. 1, which shows that the relative dead space decreases with age, and this would contribute to the high respiratory rate of the infant.

Effect of added dead space.—To evaluate these figures in terms of practical anæsthesia of children where the semi-closed method is commonly used the effect of the added dead space in the mask and connexions should be considered. The smallest mask generally used has a volume of roughly 50 ml. allowing for the volume taken up by the nose and face when it is in position, and can be used up to the age of 1 year. The natural dead space at this age is 16 ml. to which must now be added the mask volume of 50 ml., a total of 66 ml. As the tidal volume is only 79 ml. there is a theoretical alveolar ventilation of only 13 ml. with each respiratory cycle or 585 ml. per minute, or one-fifth of the normal alveolar ventilation. The next size of mask has a volume of 80 ml. and can be used up to the age of 4 years, when the child will have a tidal volume of 180 ml. and a natural dead space of 36 ml., and the corresponding figures will be 64 ml. per cycle and 1,920 ml. per minute, or half of the normal. To try and follow the changes due to this alteration of the dead space, the Rahn and Otis (1949) sampling attachment was placed between the anæsthetic face mask and the expiratory valve so that samples of the expired gas could be taken without interrupting the anæsthesia. Some dilution of the sample occurred as a reults of the high flow rate of anæsthetic gases used, 6 litres/min., and the results cannot be compared to normal expired air but they do enable the changes in a given case to be followed. The results of a typical case are seen in Table V and show that after the induction period the carbon dioxide level falls continuously.

TABLE V

Age 4 years. Pre-med.—Rectal Pentothal and Atropine
Anæsthesia—Gas, oxygen and ether

Time in minutes	0	15	25	35	45
% CO_2	2·54	3·00	2·30	2·25	2·15

Conclusion.—It has been shown that the respiratory system of the child develops most rapidly in the first two years and then more slowly during the rest of childhood. The addition of the dead space of anæsthetic apparatus to the relatively large dead space of the infant combined with the small tidal volume gives rise to a potential danger of carbon dioxide retention. The results of measurements on the expired carbon dioxide during anæsthesia

suggest that this danger can be avoided, provided that the flow rate of gases is kept sufficiently high.

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[*May* 6, 1955]

The Complications of the Trendelenburg Position [*Summary*]

By C. LANGTON HEWER, M.B., M.R.C.P., F.F.A. R.C.S.

DR. HEWER reviewed the history of, and indications for the use of the Trendelenburg position for the patient during surgery, and discussed the physiological disturbances which accompany it.

In the cardiovascular system these include hydrostatic effects leading to a rise in cerebral arterial, venous and C.S.F. pressures. The speaker drew attention to the risk of levelling up the patient too rapidly at the end of the operation if there had been much hæmorrhage or when vasomotor tone was depressed.

In the respiratory system, the upward displacement of the diaphragm by the abdominal viscera appreciably reduces the vital capacity. Thus hypoxia and hypercarbia are likely to occur unless adequate ventilation is ensured. This respiratory embarrassment is often aggravated by a distended stomach, and the passage of a stomach tube is often worth while. Secretions which nevertheless collect in the most dependent part—the naso-pharynx—should be removed by suction before levelling the table.

The risks of injury to the brachial plexus and to other parts of the body were discussed in relation to the methods employed for securing the patient in the Trendelenburg position. The usual methods of strapping the legs, or of using pelvic or shoulder rests all have disadvantages; these are obviated by a technique which utilizes the principle of skin friction, by means of a special corrugated rubber mattress with special bolsters under the neck, back and Achilles tendons (Fig. 1).

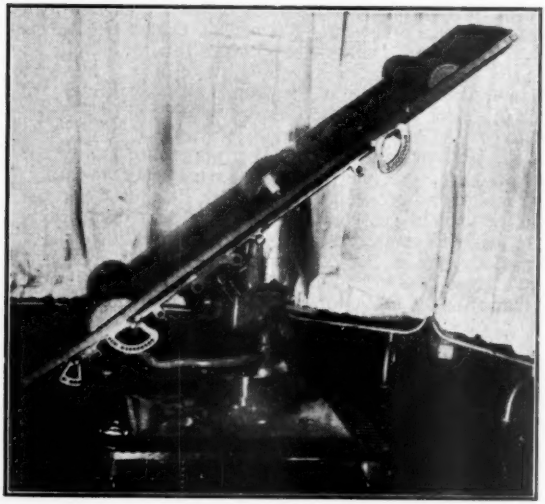

FIG. 1.—Corrugated rubber mattress hooked on to foot-end of tilted operating table. The three transverse ribbed bolsters fit respectively into the concavities of the patient's neck, lumbar region and Achilles tendons. The arms are secured on the central (lumbar) bolster, if desired.

Acknowledgment.—Fig. 1 from *Brit. med. J.*, 1955, ii, 127; by kind permission.

Dr. Hewer concluded with a description of the details and advantages of this method of fixation based on his experience with it over the past two years.

Problems of Anæsthesia in Artificial Pneumothorax

By A. R. HUNTER, M.D., F.R.F.P.S., F.F.A. R.C.S.
Manchester Royal Infirmary

THE introduction of the relaxant drugs has made anæsthesia in the tuberculous patient much more safe and satisfactory. It is now possible to use these agents with nitrous oxide and a non-volatile supplement and thus to obtain complete elimination of the toxic effects of the older anæsthetic drugs, combined with immediate recovery at the end of the operation. There is, however, one very small group of tuberculous cases where this type of anæsthesia is not always satisfactory, namely, in patients with an artificial pneumothorax induced either in the pleural or extrapleural space, or with a pneumoperitoneum. In all I have anæsthetized 100 such cases in the course of the last eight years and it is on the results of this work that the present paper is based.

At first it seemed that the primary problems in such cases were no more than those of the prevention of the spread of the disease and the preservation of an adequate respiratory exchange. In 69 cases this proved to be so. There were, however, a minority of 31 where there ensued disturbances so severe as to cause considerable anxiety. In a few instances there was an obvious and immediate threat to life.

The course of the upset.—The first sign of trouble was a rising pulse-rate which quite often reached 120 per minute within the first twenty minutes of anæsthesia (Fig. 1). When

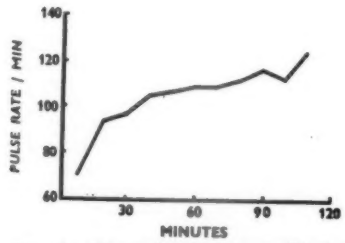

FIG. 1.—The pulse-rate changes during nitrous oxide and oxygen anæsthesia in a patient with an artificial pneumothorax.

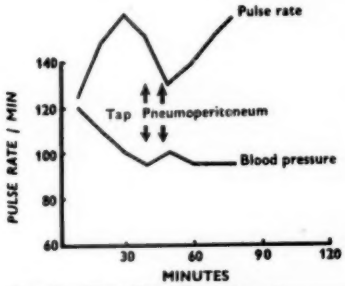

FIG. 2.—The effect of tapping a pneumoperitoneum in a patient distressed under nitrous oxide and oxygen anæsthesia.

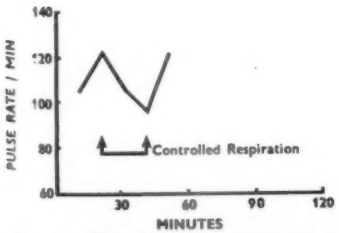

FIG. 3.—The effect of controlling the respiration on the tachycardia arising during nitrous oxide and oxygen anæsthesia in a patient with an artificial pneumothorax.

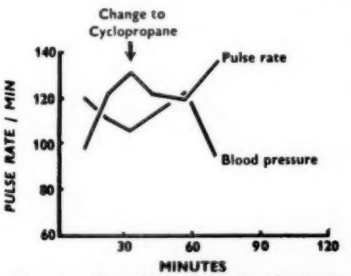

FIG. 4.—The effect of substituting cyclopropane for nitrous oxide and oxygen during anæsthesia in a patient with an artificial pneumothorax.

the operation was begun there was an obvious increase in the amount of venous bleeding in the wound and the blood shed from the veins was darker in colour than usual. Cyanosis of the arterial blood did not, however, develop except in those cases where matters progressed until there was obvious respiratory insufficiency. As the anæsthesia continued the pulse-rate rose even farther. The blood pressure was usually fairly well maintained at first but hypotension of varying degree developed sooner or later. The respiratory rate increased steadily at first. Presently respiration became laboured and in a few instances gasping in character and obviously inadequate.

The milder cases recovered spontaneously on withdrawing the anæsthetic. In the more

serious type of upset an immediate improvement in the patient's circulatory and respiratory status was obtained on tapping the air-containing cavity and removing gas from it (Fig. 2).

It was found by accident that curarizing patients who were developing this disturbance, to the point at which artificial ventilation of the lungs became necessary, greatly ameliorated this upset (Fig. 3). Presently, however, it became apparent that in some cases curarization merely postponed the evil day; for one or two patients with artificial pneumothoraces went relatively uneventfully through operation only to find themselves in extreme distress as soon as spontaneous breathing returned. Another measure which relieved the condition, again only temporarily, was the substitution of cyclopropane for nitrous oxide as the main anæsthetic agent (Fig. 4). Views concerning the safety of this agent in patients in whom the diathermy is being used have, however, changed radically in the last few years, and it has not seemed justifiable to continue to use it in these cases. It was preferable to return to nitrous oxide and to try to find an explanation of the changes which developed in these cases.

Although the initial disturbance was of the circulatory system, it seemed desirable first to eliminate respiratory insufficiency as a cause of the changes observed. Bronchoscopy was carried out on 5 extremely ill patients who had gasping respiration with indrawing of the soft parts of the neck and the patency of the bronchial tree was demonstrated beyond question. Though the vital capacities of the patients who developed the upset were undoubtedly on the low side they were not so far reduced as to threaten the respiratory exchange.

Direct leakage of gases from the lung through an unobserved bronchopleural fistula was obviously insufficient to account for the changes observed; for the disturbance appeared also in those in whom a pneumoperitoneum was present. Indeed the very worst incident of the entire series appeared in a patient in whom an aeropericardium had been induced before operation for a non-tuberculous condition, and in such a case direct leakage from the lung could not have played any part in the ætiology, especially as tapping the pericardial sac produced an immediate improvement in the patient's condition and laying open this cavity completely restored matters to normal.

The intrapleural pressure.—A consideration of the cases in which serious cardiovascular disturbances followed the induction of anæsthesia indicated that these were much more likely to appear when the cavity had recently been refilled to a pressure approximating to that of the atmosphere. It was also found by direct measurement that the pressure in a pneumothorax increased considerably after operation and anæsthesia, and that both the mean and the peak intrapleural pressures became more positive (Table I). This observation

TABLE I.—THE PRESSURES IN PNEUMOTHORACES

Pressure at beginning of operation (cm. of water)			Pressure at end of operation (cm. of water)		
Swing		Mean	Swing		Mean
−8	+4	−2	−8	+8	0
−6	+2	−2	−6	+10	+2
−9	+3	−3	−12	+18	+3
−8	−3	−5·5	−3	+3	0
−4	−1	−2·5	+4	+18	+11
−6	−2	−4	−6	+26	+10
−2	+5	+1·5	+1	+6	+3·5
Average −2·9			Average +4·2		

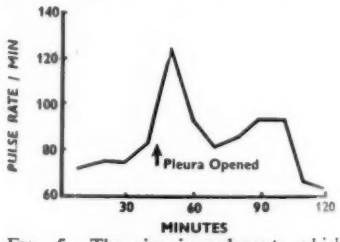

FIG. 5.—The rise in pulse-rate which follows opening the pleura during thoracotomy with the respiration controlled.

provided an indication of the mechanism by which the upset in these cases might have arisen. It is well known that there is little or no obstacle to the access of the pressure in the pleural cavity to the great veins in the mediastinum. Indeed it is to the elasticity of the lungs that the negative pressure normally there owes its origin. If the intrapleural pressure becomes more positive it is obvious that the pressure in the great veins will rise also. The pressure gradient on which the venous return depends will be abolished and blood will be dammed back in the peripheral vessels, as in fact was patently demonstrated by the venous congestion observed in these cases.

It is also interesting that in other circumstances where the venous return to the heart is interfered with, a rise in pulse-rate occurs. Thus when the chest is opened in the course of thoracotomy the pressure in one pleural cavity becomes atmospheric. There is then, even when respiration is controlled, quite often a sharp rise in pulse-rate (Fig. 5), presumably because the great veins are no longer in contact with the normally negative intrapleural pressure. A continuously rising pulse-rate regularly used to occur in the days when continuous positive pressure was used instead of controlled respiration to maintain the expansion of the lung when the chest was opened. Major interference with the return of the blood to the heart such as can occur when the intra-abdominal pressure becomes so great as to

reverse pressure gradient from the veins of the legs into the abdominal cavity, is also associated with a rise in pulse-rate (Hunter, 1950). This disturbance occurs for example when an obese patient is laid face down without adequate anterior support. It can also arise when an attempt is made to undo the lumbar lordosis by pressure on the relaxed abdominal wall of an anæsthetized patient.

Cause of rise in venous pressure.—It was not sufficient in these cases, however, to know that the cause of the upset was a disturbance of the venous pressure gradient. It was necessary also to discover how this disturbance was produced. At first mediastinal flap seemed as if it might be responsible; for chest physicians (Sewall, 1928; Penman, 1941), have long been aware that lateral respiratory movement of the mediastinum can occur with an induced pneumothorax in an intact chest, especially when the pressure in it approximates to that of the atmosphere. With this in view anæsthesia was induced in 3 patients on the X-ray table, but there was no resulting increase in the amplitude of the lateral mediastinal movement.

Suppressed straining, which Brennan (1938) has shown to have such deleterious effects on the intracranial pressure, might also have been responsible for the changes observed. Certainly the beneficial effects of curarization could readily be ascribed to such a cause. Also in the few cases where the intrapleural pressure was followed throughout the operation there was a very definite association between straining and a markedly positive intrapleural pressure. This explanation, however, failed to account for the difficulties which developed in those whose lungs had been ventilated artificially throughout the entire operation and who found themselves in trouble only when spontaneous breathing was restored. Some other factor must have been operative in them.

Gas exchange in pneumothorax.—The missing factor was found when the physiology of gaseous exchange between tissue spaces and the blood was considered. Under resting conditions the partial pressures of the gases in a pneumothorax are substantially the same as the tensions of the same gases in the blood in the underlying lung (Dautrebande and Spehl, 1922). If either of these is upset movement of molecules of gas will take place in such a direction that the balance will tend to be restored (Rist and Strohl, 1920). Thus if a pneumothorax is induced by injecting atmospheric air into the pleural space, CO_2 diffuses from the blood into the space until the partial pressure of that gas in the cavity is equal to that in the blood. Likewise, when nitrous oxide and oxygen anæsthesia is induced in a patient with an artificial pneumothorax, the tension of the nitrogen in the blood falls sharply nearly to vanishing point, while that of the nitrous oxide rises rapidly to nearly three-quarters of atmospheric pressure. A process of readjustment of the gas content of the pneumothorax therefore begins. The nitrogen in the space starts to move into the blood while nitrous oxide passes from the blood into the space. The rate of these movements is governed by the solubility of the gases in the blood. Nitrous oxide is very readily soluble. It therefore diffuses readily into the space. Nitrogen on the other hand is soluble only with difficulty and cannot therefore readily be removed. Since the two diffusion processes occur quite independently of each other there is a marked increase in the total gas content of the space, and consequently, since its volume is limited, in the total pressure there.

This physiological phenomenon provided the explanation of why the upset should be confined entirely to the period during which nitrous oxide was being inhaled and why spontaneous recovery should follow withdrawal of the anæsthetic. It also explained why the substitution of cyclopropane should improve matters, and why the upset occurred alike in the curarized and uncurarized subject.

Positive evidence to support these theoretical considerations was obtained. It was possible in 2 cases to sample the gases in a pneumothorax immediately after the induction of anæsthesia, and at the end of operation. In 3 other cases samples were taken at the end of operation only. In these cases there was either an increase in the amount of gas in the sample absorbable by concentrated H_2SO_4 or the presence of an abnormally large amount of gas showing this reaction. Apart from nitrous oxide, water vapour is the only gas likely to be present in these cavities which is absorbed by concentrated H_2SO_4. At the temperature at which the analysis was made not more than 2·4% of water vapour could be present in the samples at full saturation, and considerably larger amounts of absorbable gases were, in fact, found. It is, therefore, justifiable to presume that the entry of nitrous oxide into the space more quickly than nitrogen could escape accounts for the rise in pressure which was observed in pneumothoraces in anæsthetized patients, and therefore presumably for the rise in pulse-rate and the other signs of cardio-respiratory embarrassment which I observed.

I am greatly indebted to my colleagues of the North Western Regional Tuberculosis Service for their help and co-operation in this work, especially to Mr. A. Graham Bryce and Dr. H. G. Trayer. I also wish to thank the Department of Medical Illustration of Manchester Royal Infirmary for help in preparation of the lantern slides and Mr. Rodney Jones for carrying out the gas analysis (Table II).

TABLE II.—ANALYSIS OF GASES FROM ARTIFICIAL PNEUMOTHORACES

Operation	Percentage gas absorbed by conc. sulphuric acid: Immediately after induction	At end of operation
Thoracoplasty ..	0·0	3·1
Thoracoplasty ..	0·4	3·5
Thoracoplasty	Not determined	6·5
Lobectomy		10
Lobectomy		20

Temperature 21° C. Water vapour content at saturation point 2·4%.

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Dr. T. Cecil Gray thanked Dr. Hunter for a most interesting paper and a real contribution to the subject, but pointed out that it was a pity that he had not been able to get radiological evidence of the increase in size of the pneumothorax during gaseous anæsthesia. This would have been a pretty and convincing demonstration of the effects which he had described.

The Reduction of Operative Bleeding by T-Piece Anæsthesia

[Summary]

By J. BULLOUGH, M.B., F.F.A. R.C.S.

DR. BULLOUGH described the various types of continuous flow circuits for anæsthetic gases which include a "T"-shaped connecting piece. The aim of these methods is to provide a gas circuit which allows virtually no resistance to expiration and also minimal re-breathing.

The physiological disturbances associated with breathing against resistance were described; an important clinical manifestation of which was considered to be increased capillary and venous bleeding during surgical operations.

The speaker discussed other causes of increased bleeding during surgery, including the effects of posture, drugs and disturbances of CO_2 elimination.

A reduction in troublesome operative bleeding was claimed when a "T-piece" circuit was employed, especially in cases where posture could also be used to assist venous drainage from the wound (Fig. 1).

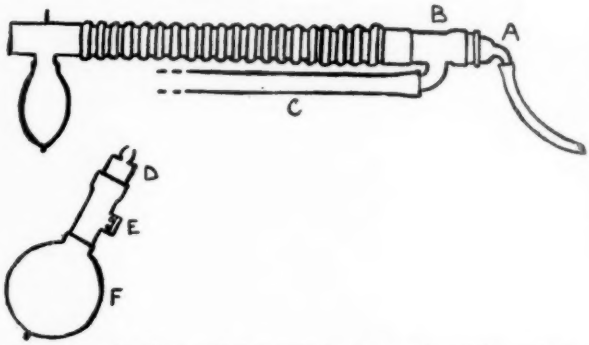

FIG. 1.—A, B, and C are attached to a semi-closed circuit (Magill attachment) to form Author's "Semi-T-Piece" circuit.

A, author's endotracheal connexion. B, author's T-piece. C, rubber tubing, ½ in. internal diameter, 3–6 ft. long. D, E, and F are attached to C for artificial ventilation of the lungs, the other bag being turned off. D, endotracheal mount. E, Heidbrink valve. F, "rebreathing" bag.

A and B are made by Messrs. Charles King.

Other advantages of this technique were simplicity, safety, the absence of clinical contra-indications and of post-operative complications.

Detailed considerations of gas circuits and technique have been published elsewhere (see References).

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Section of Dermatology

President—REGINALD T. BRAIN, M.D., F.R.C.P.

[*March* 17, 1955]

Kaposi's Multiple Pigmented Hæmorrhagic Sarcoma, almost Healed.—MAURICE GARRETTS, M.B., M.R.C.P. (for W. N. GOLDSMITH, M.D., F.R.C.P.).

Male, aged 53, native of Malta.

This man was shown to the Section on March 21, 1952 (*see* Garretts, 1952). A brief résumé of the state of affairs of that time is as follows:

History.—He first noticed dark discoloration of his hands and feet associated with pain on walking in 1948. In 1946 he had been treated with penicillin and arsenic for syphilis. At the time his skin disease began he had been exposed to cold temperatures as a labourer.

On examination.—Discrete infiltrated papules and plaques were present on both hands and both feet. The colour varied from purple to dark brown. Nodules were demonstrated along the course of the superficial veins of the left lower leg.

W.R. and Kahn negative.

Biopsy (15.1.52): Typical of Kaposi's idiopathic multiple pigmented hæmorrhagic sarcoma.

Balina (1949) and Marchionini and Götz (1950) have described their experiences in treating this disease with penicillin. 3 cases were treated (1 by Balina and 2 by Marchionini and Götz) with good results, using 4,000,000 units. Our patient was given 10,500,000 units in February 1952 without obvious effect. Since X-rays did not help the left foot, no further X-ray treatment was attempted. No objective change was noted after irradiation.

Follow-up.—Pain on walking persisted and with the onset of the winter of 1952 he complained of dyspnœa and cough due to chronic bronchitis. His chest disease and skin condition rendered him unfit for his occupation as newsvendor, or other outdoor employment and he was referred to Dr. H. J. Altschulova, the psychiatrist attached to the Department of Dermatology, as a social problem. She recommended occupational therapy which he agreed to take up. In November 1954 some dusky erythema and brownish pigmentation was all that remained. The rest of the disease with the intense cyanosis, œdema and nodules had largely disappeared.

Discussion.—An effort had since been made to assess the factors responsible for this remarkable degree of improvement. The patient claims that the disease diminished greatly a few weeks after his discharge from hospital, i.e. a few weeks after the penicillin treatment. At this time he had received 600 r X-rays to his left ankle but not to the other affected areas; so the irradiation was unlikely to have been the cause of the general improvement.

The psychiatric factors are of interest. He is a native of Malta, and comes from a poor labouring family. He left home because there was no work in 1926, when he went to North Africa. Here he worked as a farm labourer until 1936 when he went to France. In 1940 he came to this country. He has been a peanut seller, a casual labourer and a newspaper vendor. He has tried to get regular employment but has been unable to find anything suitable. Since starting occupational therapy he has shown great artistic ability and has produced the most beautiful handwork. He has found pleasure in his work for the first time in his life, has put on weight, and has started to take some pride in his appearance.

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Lymphoma with ? Poikiloderma.—MAURICE GARRETTS, M.B., M.R.C.P. (for W. N. GOLDSMITH, M.D., F.R.C.P.).

J. R., male, aged 40.

History.—Mr. J. R. first noticed a mobile painless lump on the right side of his neck in May 1952. This was removed and was considered histologically to be "a borderline case — reticulum cell sarcoma". In September 1953 he had a right otitis media and then noticed a new swelling in the right side of his neck. This was removed and Professor R. A. Willis (Leeds University) said of it "I believe it is some kind of irritative hyperplasia, related to infection of the middle ear". In October 1953 another attack of right otitis media was treated with penicillin and after two weeks a rash appeared on the face and limbs. He was then given streptomycin and after the first injection his rash became generalized and he had

swelling of the joints of his fingers. At this time he was found to have generalized lymphadenopathy with splenomegaly. He was therefore given nitrogen mustard and a short course of ACTH, a diagnosis of reticulosis having been made clinically. In June 1954 he was given a further course of nitrogen mustard and the eruption became very much worse. He arrived at University College Hospital on December 13, 1954.

Past history.—1941 (while in Local Defence Force of Hong Kong) he was taken prisoner by the Japanese. During this time he had hunger œdema, peripheral neuritis, pellagra and two attacks of dysentery. The avitaminosis cleared rapidly on vitamin B supplied by the Red Cross. 1949: Found to have tuberculosis of right upper lobe.

On examination.—Patient was thin, weak and looked very ill. The face was erythematous and the confluent erythema spread down on to the neck. The margins of this erythema were clearly defined and were darkly pigmented. The whole area was covered by very fine scaling. Two large areas of erythema were present on the back and one on the chest. These areas also showed racemose pigmentation with telangiectasia; there was slight atrophy and fine scaling. The chest was sharply demarcated and at one margin there was an overhanging fringe of thick scales. Several fingers and toes showed areas of dusky erythema, sharply demarcated on the dorsum. There was a large tender mass in the region of the right tonsil. This anchored the soft palate and was considered to be the cause of his dysphagia.

There is a large flat swelling 2 in. in diameter deep in the right submandibular region. This gland is firm, immobile and tender. Some smaller enlarged glands on both sides of the neck. Axillary glands: not enlarged. Inguinal glands: enlarged ½–1 in. in diameter. Not tender. Liver and spleen not palpable.

Examination of C.V.S., chest and abdomen revealed nothing abnormal.

C.N.S.: Limb musculature weak; muscles thin; sensation normal. Reflexes brisk.

Investigations.—Chest X-ray: signs of chronic inactive fibro-nodular tuberculosis in both upper zones. No enlarged hilar glands. Cervical spine normal. Sputum: no acid-fast bacilli seen.

Biopsies.—(1) Skin: epidermis is thin with pigmentation of the basal layers and loss of papillæ. Hydropic degeneration of basal layer. Some parakeratosis. Scanty infiltrate of lymphocytes and histiocytes around blood vessels, which are dilated and considerable fibrosis of corium and of the adventitia of the vessels.

(2) Muscles show collections of lymphocytes between the muscle bundles. These collections were not the characteristic lymphorrhages of scleroderma.

(3) Lymph node: suggestive of lipomelanic reticulosis but areas of the reticulum show a considerable degree of mitosis suggesting that a malignant change is taking place (Professor G. R. Cameron).

Electromyography: some evidence of defective neuromuscular transmission.

Blood count: Hb 97%. W.B.C. 5,400; differential count normal. W.R. and Kahn negative. Urinary creatine: 0·24 gram/twenty-four hours. No evidence of parasites in stools. Mantoux test: negative to 1:100.

Course.—He complained of pruritus and this was partially relieved by ung. antazoline. The erythema has slowly receded during the last three months.

A biopsy was requested of the peritonsillar mass but this burst and exuded pus when an intratracheal tube was inserted. A cervical gland was removed. Pus from the abscess yielded pyogenic cocci on culture and no acid-fast organisms have been isolated. The mass has only partially shrunk.

Differential diagnosis.—(1) Poikiloderma atrophicans vasculare; or (2) dermatomyositis; or (3) lupus erythematosus profundus associated with a lymphoma.

Dr. G. B. Dowling: I would support the diagnosis of dermatomyositis in this case in view of the characteristic lesions on the fingers, the general distribution of the eruption, predominantly on the face, chest and arms and also its relation to the lymphoma. A case of dermatomyositis complicating a reticulosis was published by Sheldon *et al.* in 1939. The patient was a boy who died rapidly of dermatomyositis in whom a widespread reticulosis, which could not be accurately defined, was discovered at autopsy.

REFERENCE.—Sheldon, J. H., Young, F., and Dyke, S. C. (1939) *Lancet*, i, 82.

Dr. L. Forman: I agree with Dr. Dowling that the association of dermatomyositis with malignancy of the viscera or a reticulosis is rare but significant. The fact that the skin manifestations are subsiding in this case does not negative the suggestion that the glands are malignant. Dermatomyositis may be an episode in the course of a malignant disease. In my experience dermatomyositis occurs, as in this case, after the malignancy is clinically manifest. However, Curtis, Blalock and Harrell (1952, *J. Amer. med. Ass.*, **150**, 844) state in their cases that the onset of dermatomyositis preceded the appearance of the malignant process by an average period of 18·6 months.

Dr. G. B. Dowling: In the paper by Curtis and others to which Dr. Forman refers, the statement that dermatomyositis sometimes follows visceral cancer and sometimes the reverse is made without producing evidence in the form of case histories. In 30 reports that I have read of cases in which the two diseases have been associated the malignancy has seemed clearly to have preceded the onset of dermatomyositis in all, a fact which suggests that in some way the malignant disease appears to cause the more widespread phenomena. In three of these reports it is stated that treatment of the malignant disease by operation or radiotherapy was followed by a prompt remission of the dermatomyositis.

Kyrle's Disease.—E. J. MOYNAHAN, M.R.C.P.

Mrs. L. B. Housewife, aged 52.

History.—For the past ten to twelve years she had noticed a horny eruption appearing at first on her legs and recently on her shoulders and upper chest. Some of these lesions have become infected, and the larger ones have been painful. There is a family history of a similar condition; the patient's mother has had it to a mild degree in her legs and so has her youngest brother, i.e. two of a sibship show the same anomaly.

Past history.—This patient has had treatment for a squamous cell carcinoma of her left ear, and she also has vitiligo.

Histology.—The biopsy reveals hyperkeratosis with thinning of the epidermis which has almost been penetrated in places. There are no corps-ronds or other evidence of dyskeratosis and no clefts in the epidermis. There is a dense infiltrate of round cells in the upper cutis subjacent to the hyperkeratotic areas.

This is not found in Darier's disease, and with the absence of corps-ronds it is considered that Kyrle's disease is a separate entity from Darier's disease.

Dr. R. M. B. MacKenna: I am afraid I do not know the literature very well but I am not sure that these cases do not demand more investigation than hitherto they have received. I have one woman who has shown the same condition; she has always complained of intense pain in the legs; she experiences pain when the lesions are pressed but that is a different pain from the one which constantly causes discomfort. Dr. Moynahan's patient sits up and weeps at night because of severe pain in the legs and also in the shoulders. I have the feeling that there is something deeper than the skin involved in these cases to account for that pain. I do not think the intensity of the pain in the limbs can be accounted for by this relatively small amount of cutaneous trouble. Possibly there is something happening to the nerve roots or axon sheaths at the same time.

Dr. H. Haber: Kyrle described a condition and none of the cases following have showed it in full. A case shown recently by Dr. Bettley and myself (1955, *Brit. J. Derm.*, in press) showed characteristic histologic features of Darier's disease. One section, however, also showed the morphology of Kyrle's disease. The verruca-plana-like lesions of the dorsa of the hands in Darier's condition show cracks and slits within the epidermis. Corps-ronds are not found; the latter are therefore not essential to the diagnosis of Darier's disease. There is some reason to believe that Darier's dyskeratosis and Kyrle's hyperkeratosis might be related to each other.

Dr. C. D. Calnan: I have had reason to read Kyrle's description recently and there are some points which are of interest. In his original case Kyrle took several biopsies and only one of the lesions showed this penetration. Clinically all the patients we have seen in England have been just like this case and none showed penetration.

I would like to draw attention to the very small lesions on this woman's legs. A few years ago Dr. Waddington and I showed several cases having only the small lesions. Dr. Dowling told me he had seen that several times; I believe they are genuine cases of Kyrle's disease. They are identical with what Kyrle described and all the gross cases have these lesions in addition.

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CALNAN, C. D. (1953) *Trans. St. John's Hosp. derm. Soc., Lond.*, **32**, 69.
WADDINGTON, E. (1953) *Trans. St. John's Hosp. derm. Soc., Lond.*, **32**, 67.

Dr. E. Waddington: The other interesting point about the histology is that some cases show the focal infiltrate with very little overlying hyperkeratosis. This suggests that the dermal lesion may be the primary one.

Dr. E. J. Moynahan: I had hoped to show the infiltrate. We did several biopsies in an effort to get a section which showed penetration of the epidermis but we were unsuccessful. The removal of lesions helped to relieve the pain. Some of the larger lesions were indeed very painful. Dr. R. M. B. MacKenna has drawn attention to the pain in the limbs of which she had been complaining.

Dr. Forman: I have seen a female patient who had taken arsenic in her youth and presented with numerous basal cell epitheliomata and hard keratomata on the legs. The keratomata resembled those shown in this case. Arsenic may cause peripheral neuritis, and this could account for the pain of which this patient complains.

Dr. Moynahan: The fact that her mother has the same condition may or may not exclude arsenic. I think it is an inheritable disorder of keratinization.

Dr. F. Ray Bettley: One of the illustrations which stands out in my mind in Kyrle's original paper is that of the forearms of a young woman covered with massive hard crusts or keratinous masses several inches across covering the whole of the skin—nothing like anything we have seen in all those "London cases", as Dr. Haber calls them This reminds one of a girl whom the late Dr. W. J. O'Donovan showed here. She had typical Darier's disease. The backs of her legs, chiefly the calves, were covered with enormous masses of keratinous material which we tried to remove from time to time but never succeeded in doing so. I wonder whether a biopsy has been studied of a case of that kind; when we do a biopsy of a case of Darier's disease we take a lesion from the back but I wonder what these massive keratons look like histologically.

REFERENCE

KYRLE (1916) *Arch Derm. Syph., Berl.*, **123**, 466.

The following cases were also shown:

(1) **Congenital Morbus Cordis and Lupus Erythematosus in a Boy Aged 6 Following Treatment with Antibiotics and Controlled by Chloroquine.** (2) **Pseudoxanthoma Elasticum and Lichen Planus Linearis.**—Dr. BRIAN F. RUSSELL.

Pseudoxanthoma Elasticum.—Dr. W. FRAIN-BELL (for Dr. J. E. M. WIGLEY).

Dermatitis Repens.—Dr. H. T. H. WILSON.

(1) **Eosinophilic Granuloma of Face.** (2) **Epidermolysis Bullosa.** (3) **Peri-ungual Fibromata in a Case of Adenoma Sebaceum.**—Dr. A. AITKEN ROSS.

(1) **Prurigo Nodularis.** (2) **Monilethrix.**—Dr. E. J. MOYNAHAN.

Nævo-xantho-endothelioma.—Dr. M. FEIWEL.

Tuberculides.—Dr. R. G. HOWELL.

Orf.—Dr. N. A. THORNE and Dr. P. J. FEENY.

A film entitled **Clinical Signs of Frambœsia Tropica** was shown by Dr. IVAN POLUNIN.

[*April*, 21, 1955]

Turban Tumours of Scalp, with Bony Erosion (Cylindroma).—J. B. LYON, M.B., M.R.C.P.

Mr. P. C., aged 59. Agricultural labourer.

History.—Twenty-five to thirty years since red specks first began to appear, growing very slowly over the years. Three years ago, a very large one developed over the posterior portion of the scalp, attaining the size of a large Jaffa orange. Two years ago a small one was noticed on the left flank and another on the right upper sternum.

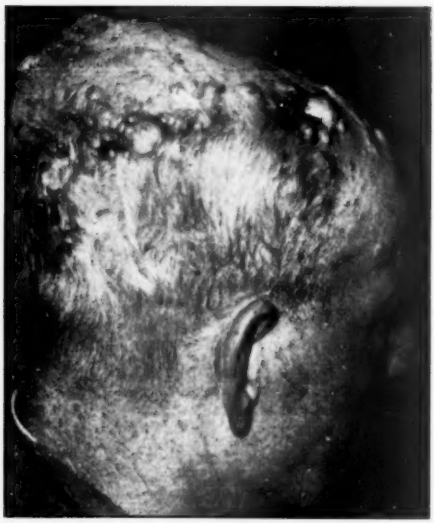

FIG. 1.—Photograph of scalp showing multiple small tumours and one large tumour prior to excision.

Family history.—Parents, 3 brothers and 1 sister not affected.

On examination.—Multiple tumours of scalp and forehead (Fig. 1); some reddish in colour, others of normal skin hue and varying in size from a few mm. to several cm., some sessile, some pedunculated. A scar is present over the left occipito-parietal region from excision of the largest tumour which measured about 10×8 cm., was soft, fluctuant, hæmorrhagic and at operation was found to have penetrated the skull down to the dura. Other scars are seen on the left loin and right sternum from excision of 2 small similar tumours.

Investigations.—X-ray of skull (7.10.54). There is a large soft-tissue mass situated over the post-parietal region on the left side; calcification is seen within the tumour. Deep to it there is a large area of bone destruction. Histology: (1) Of small scalp tumour: It

is composed of well-defined masses of basophilic epithelial cells surrounded by thick hyaline basement membranes. The appearance resembles ducts distended by tumour cells. Mitotic figures are scanty. The appearances are those of a sub-epidermal basal cell growth arising from pilo-sebaceous epithelium—the "Turban tumours" of Ronchese. (2) Of largest scalp tumour: Sections have been made of 2 pieces of this large irregular mass of tissue; both show extensive necrosis with hæmorrhage and inflammatory cell infiltration. There are, however, large areas of surviving tumour tissue in the deeper layers especially. These are highly cellular but show no very pronounced difference from the last biopsy material from the scalp and trunk except that the cell masses tend to be more diffuse though the glandular formations are again very evident. Mitoses are scanty.

Comment.—The interesting feature is the very large calcified tumour over the occipito-parietal region which had penetrated down to the dura mater, and yet had retained its benign histological character. The subject has recently been reviewed by Evans (1954).

I am indebted to Dr. R. U. F. Kynaston and Mr. G. F. Langley for permission to show this case.

REFERENCE.—EVANS, C. D. (1954) *Brit. J. Derm.*, **66**, 434.

Dr. B. C. Tate: Was it considered that the bone was eroded simply by pressure or by infiltration into the bone?

Dr. J. B. Lyon: I think by pressure.

Dr. C. H. Whittle: Is this tumour radio-sensitive? I believe some turban tumours are.

Dr. J. C. Belisario: I have treated several cases and they exhibited some degree of radio-sensitivity. Surgery, however, is the treatment of choice.

Colloid Milium.—H. T. H. WILSON, M.D., M.R.C.P.

Woman, aged 35, attended hospital about six weeks ago for treatment of warts on the hand. It was noticed at the time that there was a yellowish, slightly translucent, papular eruption on the backs of both hands. This had been present since the age of 22. There was also a limited area of pigmentation on the face but no yellowish papule. She thought that her skin was rather drier than it used to be but apart from this had had no skin disease except the condition described. She had had various childish complaints, also pyelitis when aged 6 and she underwent appendicectomy last year. She had lived in South Africa or Rhodesia all her life. Her father, who had lived in Africa most of his life, had had a similar condition of his hands since age 25; the mother was unaffected. One brother aged 30 had been similarly affected since age 20, and a sister aged 23 was showing early signs of a similar condition. Another brother and sister were unaffected.

Histology (Dr. H. Haber).—Separated by a narrow zone of normal collagen, there are several foci consisting of a fissured mass of homogeneous material containing a few nuclei. The histology is quite characteristic of colloid milium.

Discussion.—About fifty cases of colloid milium have been reported since 1866. This case belongs to the commoner type referred to by Arnold (1943) as colloid pseudo-milium. It consists of small superficial discrete lesions on the face or backs of the hands. A deeper more diffuse type of eruption is much rarer.

The fact that the lesions are almost confined to exposed parts and that most of the reported cases have come from Italy, the South of France or the Southern States of America suggests that sunlight is an important factor in its causation.

The patient shown had spent all her life in South Africa or Rhodesia. Her case is interesting because her father suffers from a similar condition and also from multiple rodent ulcers. A sister and brother are also reported to have colloid milium. The exact nature of the colloid material is not known with certainty. It is believed to be a combination of degenerated collagen and degenerated elastin.

REFERENCE.—ARNOLD, H. L. (1943) *Arch. Derm. Syph., Chicago*, **48**, 262.

The following cases were also shown:

Kaposi's Sarcoma.—Dr. R. H. MARTEN (for Dr. J. E. M. WIGLEY).

Generalized Morphœa.—Dr. S. GOLD.

Lichen Sclerosus et Atrophicans.—Dr. E. J. MOYNAHAN.

Naevus of Ota.—Dr. H. HABER and Dr. M. FEIWEL.

Lupus Erythematosus (Subacute Systemic).—Dr. W. FRAIN-BELL (for Dr. L. FORMAN).

Hypertrophic Lichen Planus Treated by Local Injection of Hydrocortisone.—Dr. J. S. PEGUM.

Acneiform Papulonecrotic Tuberculide.—Dr. R. H. MEARA.

A case of **Torulosis** was reported by Dr. I. S. HODGSON-JONES.

[*May* 19, 1955]

Idiopathic Steatorrhœa.—P. D. SAMMAN, M.D.

Mr. R. C., aged 61, attended Westminster Hospital since 1949 with a rash which began on his hands, spread to his feet and legs, and later became generalized. He was an in-patient for six months in 1949 and at that time was found to have a macrocytic anæmia. The hæmoglobin was as low as 40%; R.B.C. 1·5 million and colour index 1·3.

It was not until 1952 that he first had diarrhœa with pale watery stools, which pointed to steatorrhœa as the cause of this anæmia. The stools were found to contain 20 grams of total fat per 100 grams dried fæces. Fat absorption was 68% (normal 90%). Treatment with folic acid and a gluten-free diet produced marked improvement in his general condition but at that time the skin did not improve to any extent. In 1954 the skin steadily improved but during the present year it has gradually deteriorated again.

The appearance of the skin lesions has always been of a dry scaly condition, widely scattered, some quite small, others larger and tending to form rings. At present one of these rings is present on the inner side of the right elbow. The individual lesions have been slightly raised above the surface and are red in colour. The areas most affected have been the arms and legs but at times the trunk has also been involved. The facial appearance is rather characteristic with pale sunken cheeks and an expression of sadness. The scaly lesions, however, have not occurred here. The condition has always been very resistant to local treatment. Around the elbows it has looked at times like dermatitis herpetiformis but without true vesicle formation.

FIG. 1.—Right elbow, May 1955.

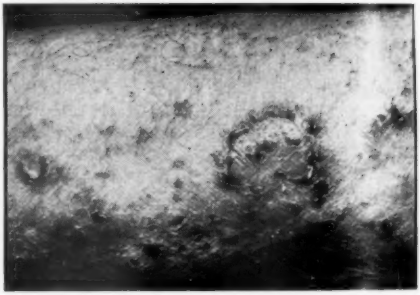

FIG. 2.—Close-up of right elbow, May 1955.

Comment.—Under the title idiopathic steatorrhœa a condition of the skin is shown in the Nekam Atlas which appears similar to the present case. The photograph in the Atlas was submitted by Dr. Donald Hunter. A number of other skin conditions have been described in connexion with steatorrhœa. It is probable that the various skin conditions are associated with one of the numerous deficiencies that occur in this condition.

(I am indebted to Dr. J. L. Franklin and Dr. R. I. S. Bayliss for permission to show this case.)

The President: It is a very unusual case and it will be interesting to hear if this is the usual eruption associated with steatorrhœa or whether it merely represents degenerative changes in the skin.

Dr. L. Forman: Some time ago I saw an elderly man, a patient of Dr. A. C. Hampson's, at Guy's, who was suffering from a widespread prurigo, with lichenification and pigmentation. He had a macrocytic anæmia. The stools were frequent and contained an excess of unsplit fat. When given crude liver extract and vitamin B_2 complex he made a considerable improvement. It was thought that the skin change was due to a deficiency either of vitamin B_2, fatty acid, or calcium.

Dr. R. D. Sweet: I have a case which matches this one in almost every detail. He is a young man of about 40 whom I have been seeing for four years. He has had idiopathic steatorrhœa for considerably longer and this was helped a little by folic acid and a gluten-free diet, but these measures did not prevent his eruption from appearing or control it in any way. It resembled dermatitis herpetiformis but was not controlled by sulphapyridine. Diaminodiphenylsulphone did seem to do some good but unfortunately it intensified his already severe macrocytic anæmia. About nine months ago he was put on small doses of cortisone, which not only vastly improved his anæmia but also completely controlled his skin eruption.

The close similarity between my case and Dr. Samman's makes me feel that they must represent a true clinical entity.

Dr. Brian Russell: Idiopathic steatorrhœa is a disease in which metabolic disturbances are both numerous and complex. A variety of eruptions may occur with it. I have seen two such patients

recently. The first was diagnosed by Dr. Louis Sefton and had previously been regarded as a case of endogenous depression. There was a pellagroid dermatitis and tetany. The other patient who was under the care of Dr. Kenneth Perry had an erythrodermia with secondary infection and a hæmoglobin percentage of 15. Neither patient had lesions which in any way resembled those of Dr. Samman's patient.

The President: I do not think we can deduce from the descriptions that there is any specific eruption in steatorrhœa.

Facial Hemiatrophy.—PETER BORRIE, M.D., M.R.C.P.

D. R., girl aged 8.

History.—In February 1953 a mauve line appeared running down the forehead to the right of the mid-line. Over the next six months this spread upwards into the scalp and downwards and outwards over the right half of the face, leaving the skin behind it pigmented, shiny and sclerotic. No further spread of the condition has since occurred, but at the beginning of 1954 atrophy of the skin and subcutaneous tissues commenced in the forehead and has extended to almost the whole of the sclerotic area.

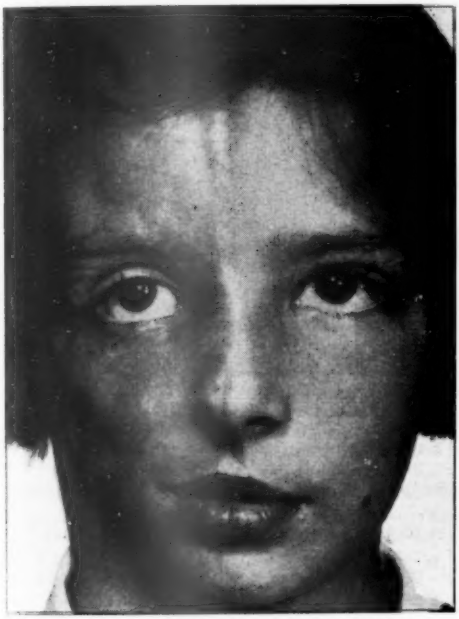

FIG. 1.—Facial hemiatrophy, May 1955.

Past history.—Severe attack of measles two months before onset of skin condition.

Family history.—Not relevant.

On examination.—The skin of the whole of the right half of the face is pigmented and atrophic with the exception of a small area in front of the ear which is still sclerotic. The subcutaneous tissue and muscle are also affected by the atrophic process. A band of cicatricial alopecia 2 in. wide and 4 in. long runs back over the scalp to the right of the mid-line. The muscle, though not the epithelium, of the right half of the tongue is atrophic but the palate and pharynx are normal. There is no sensory loss or paralysis (Fig. 1).

Investigations.—X-ray of skull: no bony abnormalities. X-ray of the teeth and mandibles: delayed development of right teeth and mandible.

Comment.—Although some cases of facial hemiatrophy exhibit at some stage of their evolution cutaneous sclerosis the condition is clearly not a variety of scleroderma. Extrafacial patches of atrophy of an identical type occur and in neither of the examples shown before this Section recently (Mitchell-Heggs and Borrie, 1949; Bettley, 1950) was there any sclerodermatous change. It is the subcutaneous tissue which is primarily and constantly affected in this group of atrophies, as Wartenburg (1945) points out, and thus they are clearly separate from both the dermal atrophies and scleroderma.

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Case for Diagnosis.—E. N. M. JOHNSTON, M.D. (for H. J. WALLACE, M.D.).

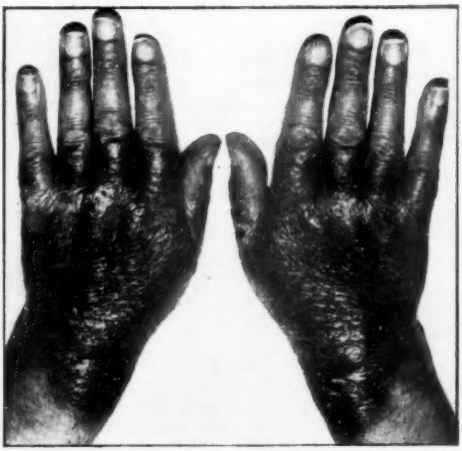
Man, aged 52. Since 1939 bluish discoloration of the skin of the hands and feet has been constant. The elbows, knees, buttocks and penis have also been involved. Swelling and painful burning of the hands and feet have occurred on exposure to cold with subsequent splitting of the skin. He was treated with mercury, bismuth, arsenic and radiotherapy without benefit and was seen in 1945 by Drs. H. W. Barber and A. C. Roxburgh. A diagnosis of atypical lichen planus was apparently confirmed by biopsy.

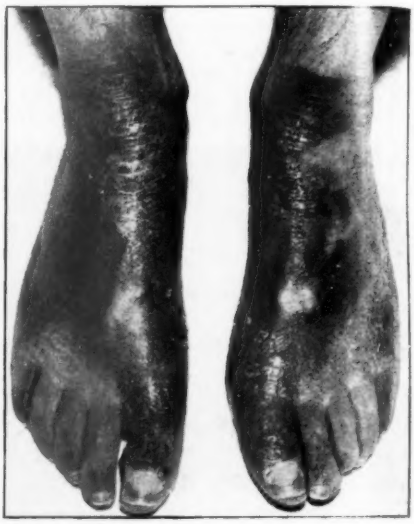
Iritis of the left eye which began two months ago is responding to local cortisone. At

this time a supraclavicular swelling was noted. Since 1947 he has suffered from dysphagia, considered to be due to an œsophageal stricture.

On examination.—General condition good. B.P. 130/85. Liver edge is clearly felt on inspiration. Spleen not felt.

A firm mobile walnut-sized swelling is present in the right supraclavicular region. No other glands are palpable.





FIGS. 1 and 2.—Hands and feet, May 1955.

Skin lesions.—Distributed on hands, feet, buttocks, knee, elbows, glans penis and prepuce. On the hands and feet there is bluish scaling atrophic skin with some splitting. Skin flexures are spared in some areas.

Recently, discoloured nodules and slight infiltration have appeared on the feet and toes. Brownish pigmentation is seen on diascopy.

The lesions on the buttocks are similar to those on the knees. The glans shows bluish discoloration with scaling.

Investigations.—Chest X-ray normal. Blood count: Hb. 108%; W.B.C. 8,600/c.mm., neutros. 63, lymphos. 35, monos. 2%. E.S.R. 23 mm. in 1 hour (Westergren). Plasma proteins: Total 8·5, albumin 5·1, globulin 3·4 grams %. Mantoux 1/1000: Strongly positive.

5.10.55: Result of biopsy: Dr. Whimster reports that the histology of skin of an affected toe shows a very heavy infiltration of the dermis, and to a less extent of the epidermis, with cells which are mainly of the lymphocyte series.

The changes possibly indicate an early reticulosis but there is no positive evidence of the latter.

Treatment.—A full course of penicillin is being given.

The following cases were also shown:

Alopecia Areata.—Dr. L. FORMAN.

Kaposi's Sarcoma.—Dr. R. G. HOWELL (for Dr. G. B. MITCHELL-HEGGS).

Pityriasis Lichenoides et Varioliformis.—Dr. P. D. SAMMAN.

? Sarcoidosis.—Dr. S. P. HALL-SMITH.

Monilethrix Regrowth After Treatment with ACTH.—Dr. E. J. MOYNAHAN.

Lentigo Maligna Associated with Pre-cancerous Melanosis Bulbi.—Dr. I. A. MAGNUS (for Dr. E. J. MOYNAHAN).

Thibierge-Weissenbach Syndrome (Scleroderma with Calcinosis).—Dr. J. C. FIRTH (for Dr. R. J. HARRISON and Dr. M. FEIWEL).

(1) **Sclerœdema.** (2) **Pemphigus Foliaceus.** (3) **Intra-epidermal Epithelioma.**—Dr. D. L. WILLIAMS.

Case for Diagnosis. ? Lupus Erythematosus. ? Lichen Planus. ? Erythema Figuratum Perstans.—Dr. THERESA KINDLER.

Erythrasma.—Dr. C. M. RIDLEY (for Dr. J. S. PEGUM).

Section of Experimental Medicine and Therapeutics

President—Professor CLIFFORD WILSON, D.M., F.R.C.P.

[*May* 10, 1955]

DISCUSSION ON THE RENAL TUBULES

Dr. H. Harris:

Genetically Determined Disorders of the Renal Tubules

IN recent years a number of genetically determined disorders have been found to involve changes in renal tubule function. They include conditions as widely different clinically and biochemically from one another as cystinuria, vitamin-D resistant rickets, galactosæmia, Wilson's disease, and the Fanconi syndrome. However, it is perhaps of interest to consider them together in order to see what features they have in common, how far they can be understood in terms of current genetical concepts, and what light they throw on the way genes influence normal physiological processes in the kidney.

Active reabsorption by the renal tubule cells of a large number of different metabolites from the glomerular filtrate is known to occur. There appears to be a complex of different processes each handling one substance or a group of related substances, but no doubt integrated together at various levels. Abnormal genes are known which lead to a disturbance of this complicated transport system at different points so that the reabsorptive capacity of the tubules for particular metabolites or groups of metabolites is diminished.

In some of these disorders the disturbance in renal tubular function is highly specific for a small group of metabolites or even a single metabolite, while the reabsorption of other substances goes on perfectly normally. For example in cystinuria there is a specific abnormality in the reabsorption of four amino acids: cystine, lysine, arginine and ornithine (Stein, 1951; Dent, Senior and Walshe, 1954). All the many other amino acids present in the glomerular filtrate are reabsorbed normally as are other substances. Similarly in renal glycosuria the defect is in most cases confined to glucose reabsorption (Govaerts, 1952) and in one type of vitamin-D resistant rickets to phosphate reabsorption (Dent, 1952).

On the other hand in some conditions a more generalized disturbance of tubular function is encountered. In the Fanconi syndrome (Dent, 1952) a disturbance in tubular reabsorption occurs which involves many amino acids, glucose, phosphate, water and perhaps bicarbonate. In Wilson's disease the reabsorption of a large number of amino acids (Stein, Bearn and Moore, 1954), often glucose (Bearn and Kunkel, 1954), and occasionally perhaps uric acid (Bishop, Zimdahl and Talbott, 1954), may be affected.

Thus it is apparent that abnormal genes may lead to dysfunction of the renal tubule transport system at many different levels.

Now each of these conditions appears to be determined by an autosomal gene, though of course it is a different one in each case. We can represent the genetical situation in fairly simple terms in the following way. If at a particular chromosomal locus there may occur in a population a normal gene A and an abnormal gene a, then since each person will carry two such genes, one derived from each of his parents, three genetically distinct types of individual can occur and these may be represented as

AA ; Aa ; aa

Individuals carrying the abnormal gene in single dose (Aa) are called heterozygotes, and they will be found very much more frequently in the population than individuals who carry it in double dose (aa), who are called homozygotes.

In certain conditions, for example Wilson's disease (Bearn, 1953), the Fanconi syndrome (Bickel and Harris, 1952), and one type of cystinuria (Harris and Warren, 1953), the disorder is only observed if the abnormal gene is present in double dose (i.e. in aa individuals). The heterozygotes Aa appear normal. Such conditions are called recessive and give rise to very characteristic pedigrees. The abnormality is often found in more than one of a group of brothers and sisters, but very rarely in the parents, children and other relatives of affected patients. There is also an increased incidence of parental consanguinity.

Other conditions arise if the abnormal gene is present only in single dose (i.e. in Aa individuals). This appears to be the situation in renal glycosuria and in certain forms of vitamin-D resistant rickets. An entirely different type of pedigree is found. The disorder occurs in several generations of the same family, apparently being transmitted directly from an affected parent to a proportion of his or her offspring. What effect a double dose of such a gene would have we are often in no position to say. The appropriate type of mating which would give rise to such individuals must be rare and so far in the case of renal glycosuria, or of resistant rickets, it has not been observed. On general grounds, however, we would expect that such homozygotes would show the same kind of abnormality as the heterozygotes but in a greatly accentuated form.

In very favourable circumstances we have been able to identify all three possible genotypes (Harris, Mittwoch, Robson, and Warren, 1955). This is the situation in one group of families in which cystinuria occurs. In these families three types of individual may be recognized; those with a complete or nearly complete failure to reabsorb cystine, lysine, arginine and ornithine from the glomerular filtrate, those with only a partial failure of reabsorption of cystine and lysine, and those with normal tubular function. The homozygotes (aa) excrete all four amino acids in grossly abnormal amounts and frequently form cystine calculi. The heterozygotes (Aa) excrete cystine and lysine in moderately abnormal amounts and only very occasionally form calculi, because the cystine concentration rarely rises to saturation level.

Now a gene can be regarded as a highly differentiated segment of a chromosome with a specific structure and specific properties. Chemically it appears to be a desoxyribose-nucleoprotein. Each normal gene is thought to have some particular biochemical function in the cell and hence in the body as a whole. Very often genes appear to be concerned in some way with the synthesis of enzymes and if an abnormal gene occurs it may not be able to carry out this synthesis in the usual way. The resulting consequences for the organism will depend on the nature of the metabolic process mediated by the particular enzyme concerned.

In a condition such as cystinuria all the clinical and biochemical findings can be explained in terms of a highly localized disturbance in renal tubular functions. It is reasonable then to postulate that the normal gene at this locus is directly concerned in some way with a specific process in the active transport of the four amino acids involved, across the tubule cells. Possibly it plays a part in the synthesis of a particular enzyme necessary for this. The process would fail in individuals homozygous for the abnormal gene because the appropriate enzyme might not be formed, and would partially fail in one kind of heterozygote because the enzyme might only be present in limited amounts. This kind of hypothesis may also be applicable to the highly specific tubular disorders found in certain types of renal glycosuria and in vitamin-D resistant rickets.

An abnormal gene may, however, lead to renal tubular dysfunction in a rather more indirect way. If, for example, there occurs in the normal course of intermediary metabolism a series of reactions which can be written schematically as follows

$$A \xrightarrow{\alpha} B \xrightarrow{\beta} C \xrightarrow{\gamma} D \xrightarrow{\delta} E$$

then a genetically determined failure to synthesize enzyme β could lead to the accumulation in the body of large amounts of metabolite B, which under normal circumstances may be present in only small quantities. Such an accumulation of a particular metabolite in the body could perhaps lead to widespread toxic effects in many tissues, possibly far removed from its site of origin. The renal tubules could in this way be damaged as a result of the absence of an enzyme normally present, say, in the liver.

There is evidence that something of this sort is happening in several clinical conditions in which renal tubular disturbances occur. In galactosæmia for example, there is a marked inability to metabolize galactose completely, possibly because of the absence or relative deficiency of the enzyme which normally converts galactose-1-phosphate to glucose-1-phosphate (Schwartz, Goldberg, Komrower and Holzel, 1955). Infants with this condition fed on a milk diet have a high galactose level in their blood and possibly an accumulation of galactose-1-phosphate in their tissue cells. They fail to thrive and to gain weight, their livers enlarge and they develop cataract. These gross manifestations of the disease probably represent toxic effects in different tissues due to the accumulation of galactose or galactose-1-phosphate, because they do not occur if such children are fed with a galactose-free diet. The disturbance in renal tubular function which is found in these children is probably a more subtle manifestation of the overall toxic upset. There is a relative inefficiency in the reabsorption of a number of amino acids from the glomerular filtrate, and consequent aminoaciduria. The aminoaciduria will slowly disappear if a galactose-free diet is given

and the renal clearance of amino acids returns to normal (Cusworth, Dent and Flynn, 1955). Thus the functional disturbance in the kidney is reversible.

A somewhat analogous sequence of events probably accounts for the renal tubular disorder encountered in Wilson's disease. Here the primary abnormality is a disturbance in copper metabolism which leads to a widespread deposition of copper throughout the body. The various clinical and pathological features of the condition can probably be attributed to the toxic effects of this accumulation of copper, and the renal tubules are probably damaged along with many other tissues (Cartwright *et al.*, 1954).

A distinction may thus be drawn between abnormal genes which lead directly to disturbances in tubule function because their normal counterpart is in some way intimately connected with this, and those which do so only indirectly. This may perhaps serve as a useful framework in the investigation of such disorders. However, in the conditions which have been discussed, much more research will be required before we can be certain of what is going on.

It must also be emphasized that there exist a number of other conditions with rather complex features including renal tubular disorders, where we are still very far from having any clear idea at all what the primary action of the gene is likely to be. Notable among these is the Fanconi syndrome.

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Dr. J. Anderson:

The Parathyroid and Tubular Reabsorption of Phosphate

Phosphate clearances in children and adults especially at low plasma phosphorus concentrations are very variable. This has made clinical tests based on these clearances difficult to interpret. Because of this the tubular maximum reabsorptive capacity (Tm) for phosphorus (Tm P) was thought to be a more suitable measurement in patients with altered parathyroid activity.

A method of determining the Tm P by means of a single three-hour phosphate infusion was described (Anderson, 1955).

Tm P determinations in 4 patients with primary hyperparathyroidism showed that it was low before operation and returned towards normal post-operatively. In one patient it took about one year to return to normal. The reason for this delay is being further investigated.

Two patients with secondary hyperparathyroidism associated with chronic renal failure had their Tm P determined at a time when the pathognomonic radiographic bone changes were marked. Both had low glomerular filtration rates (G.F.R.) and very low Tm P. The significance of the low Tm P when associated with a low G.F.R. was difficult to assess.

Two patients with post-operative hypoparathyroidism had the Tm P determined at a time when the plasma calcium concentration was low and they had tetany. Full clinical, biochemical and ECG control during the infusion was undertaken because of the alleged danger of precipitating irreversible tetany. The Tm P was higher than normal.

This work suggests that excess parathyroid secretion lowers the Tm P and that in its absence the Tm P is higher than normal. The findings in secondary hyperparathyroidism were not conclusive. Thus in man parathyroid hormone has a constant depressive action on the renal tubular reabsorption of phosphate.

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Dr. M. D. Milne:

Potassium-losing Nephritis and Primary Aldosteronism

Although the syndrome of familial periodic paralysis has been recognized for over a hundred years (Cavaré, 1853), its cause was a complete mystery prior to the classical investigations of Aitken *et al.* (1937). It was then shown that the attacks of muscular paralysis were associated with a profound fall of serum potassium, and could be precipitated by a large carbohydrate meal or by injections of insulin. Danowski *et al.* (1948) proved that there was no actual loss of potassium from the body, the fall in serum potassium being due to transfer of this cation from the extracellular to the intracellular compartment.

Many examples of hypokalæmic paralysis are, however, due to conditions associated with actual potassium depletion. Brown *et al.* (1944) described cases of renal disease in which there was excessive urinary potassium loss, the patients often presenting as sporadic cases of periodic paralysis. Further examples of this condition, now usually termed "renal tubular acidosis", have been described by Albright *et al.* (1946), Milne *et al.* (1952), and Fourman and McCance (1955). There is invariably a reduced ability to acidify the urine, associated with a low urinary ammonia content and increased excretion of both potassium and calcium. The hypercalciuria often causes nephrocalcinosis and rickets or osteomalacia. A similar renal defect leading to hypokalæmia has been described in both the adult and the infantile forms of the Fanconi syndrome (Milne *et al.*, 1952; Bickel *et al.*, 1953), and in some cases of uretero-sigmoidostomy (Diefenbach *et al.*, 1951). All these conditions show the common feature of a systemic acidosis with reduced serum bicarbonate, associated with a neutral or only faintly acid urine.

More recently interest has been focused on cases of hypokalæmia due to excessive urinary potassium loss, but with a normal or high serum bicarbonate (Earle *et al.*, 1951; Evans and Milne, 1954). It has long been recognized that in potassium depletion there is a tendency to extracellular alkalosis with a raised serum bicarbonate. This has been shown to be of metabolic rather than of renal origin, being due to transfer of hydrogen ion from the extracellular fluid to the body cells (Cooke *et al.*, 1952; Black and Milne, 1952). If the hypokalæmic alkalosis due to potassium depletion is greater than the acidosis caused by renal tubular dysfunction, an increase of serum bicarbonate occurs.

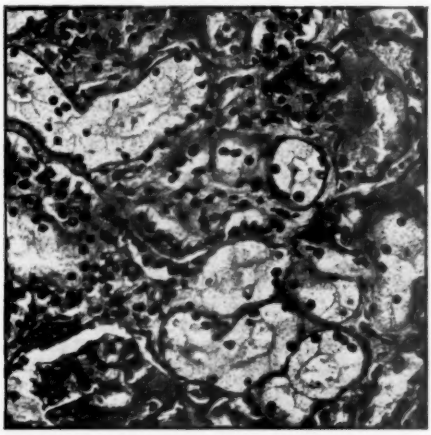

FIG. 1.—Section of kidney from a case of steatorrhœa showing the typical changes produced by severe potassium deficiency. There is vacuolization of cytoplasm and pyknosis of nuclei of renal tubular cells. × 210.

Severe potassium deficiency can of itself cause both structural and functional renal defects. The former, which has been termed "clear-cell nephrosis" by American pathologists (Follis *et al.*, 1942; Perkins *et al.*, 1950), consists of vacuolization of the cytoplasm of both proximal and distal tubule cells with pyknosis of nuclei. The lesion, which is more severe in the proximal tubule, may progress to cellular necrosis. A typical example from a case of steatorrhœa complicated by severe and prolonged potassium deficiency is shown in Fig. 1. Schwartz and Relman (1953) have described associated renal functional defects which may closely simulate those seen in primary kidney disease, i.e. defective urinary concentration power with isosthenuria, reduction of glomerular filtration rate and renal plasma flow, rise of blood urea, and proteinuria. More recently Clarke *et al.* (1955) have shown that relatively slight degrees of potassium depletion can impair the ability of the kidney to secrete a maximally acid urine.

Conn (1955) has shown that many of the cases of hypokalæmic alkalosis secondary to increased urinary potassium loss are in fact due to adrenal rather than renal disease, and has called the condition "primary aldosteronism". At least 4 more cases of this disease have been recognized in the short period since its first description (Conn, 1955). The primary abnormality is an increased secretion, usually due to an adrenal cortical adenoma, of the potent mineralo-corticoid, aldosterone. This hormone causes retention of sodium and increased output of potassium by the kidneys. Severe potassium depletion is produced which results in the characteristic renal abnormalities already described. These have

misled previous workers (Earle *et al.*, 1951; Evans and Milne, 1954) who interpreted the condition as being due to primary renal disease. Conn has shown that, in the cases due to a unilateral adrenal cortical adenoma, complete cure may be expected after surgical excision of the tumour. Post-operatively, there is retention of potassium and loss of sodium, with restoration of serum electrolytes to normal values. Hypertension with proteinuria is a usual feature and is also relieved by operation.

The adreno-genital syndrome, Cushing's syndrome, and primary aldosteronism may each be caused by a secreting adrenal cortical tumour. Intermediate states showing features of both the first and second conditions are known to occur, and possibly all cases of "primary aldosteronism" will not prove to be identical with those already recognized. It is certain that some cases of hypokalæmic alkalosis with excessive potassium loss in the urine are due to primary renal and not to adrenal disease. In the present state of knowledge criteria of differential diagnosis can only be speculative. Renal biopsy and radiography of the adrenals after peri-renal air insufflation will obviously be of value. Some of the florid cases of primary aldosteronism so far described have shown persistence of a low serum potassium despite very large oral potassium supplements, but milder examples of the syndrome may conceivably occur. The demonstration of excess aldosterone in the urine is technically difficult, and at present available only to certain specialized centres. Analysis of saliva and sweat for sodium and potassium has been claimed to be of value, cases of primary aldosteronism showing an abnormally low Na/K ratio (Conn, 1955). The value of this method is, however, reduced by the wide range of the ratio in normal subjects. In the case of saliva, this has recently been quoted as varying from 0·15 to 2·10 (Pawan, 1955).

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Dr. **E. M. Darmady** and **Miss Fay Stranack:**

Microdissection of Renal Tubules

The microdissection of the nephron is not a new procedure and has been used extensively by Oliver to study the pathological changes of the kidney. The technique consists of macerating the representative portions of the kidney in concentrated hydrochloric acid for thirty-six to forty-eight hours, and, after washing off the acid and floating the tissue in water, separating the nephrons one from another under low power dissecting microscopes (Oliver, 1939; Darmady and Stranack, 1954).

Our object in these investigations has been to correlate the biochemical changes found in the kidney in life with the lesions we have found in the nephron. Harris has already discussed those renal tubular defects which appear to have a genetic origin, and we would like to show here the renal lesions we have found in one of those syndromes, namely the Fanconi syndrome. Findings from 3 cases have already been reported (Clay *et al.*, 1953; Darmady, 1954). We now wish to record 3 further cases. In Cases I, II, III, and V the lesions were identical in that the glomerulus was joined to the proximal tubule by a narrow elongated

neck lined by flat regular epithelium (*see* Fig. 1). In Cases IV and VI the changes were a little different, the narrowing of the neck was not so marked and the epithelium was flattened throughout the length of the proximal tubule. It was thought that it was shorter than normal and the width of the tubule reduced (*see* Fig. 2). It is perhaps of interest to note that in three cases of Kinnier Wilson's disease (hepato-lenticular degeneration) we were unable to find narrowing of the neck, although aminoaciduria was present in life.

We would like to turn now to another syndrome which would seem to have a genetic basis, that of congenital familial nephrosis. The first family consisted of two male siblings, the children of first cousins. Shortly after birth they were found to have a nephrotic-like syndrome and died at the age of 5 months and 6 months, respectively. Microdissection of both kidneys showed changes which were very similar to that of the Fanconi syndrome in that there was a narrow elongated neck of the proximal tubule. The proximal tubule itself showed gross "ballooning" and flattening of the epithelium with dilatation of the lumen.

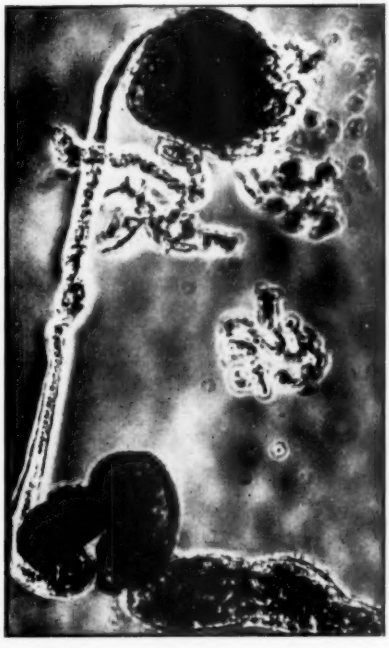

FIG. 1.

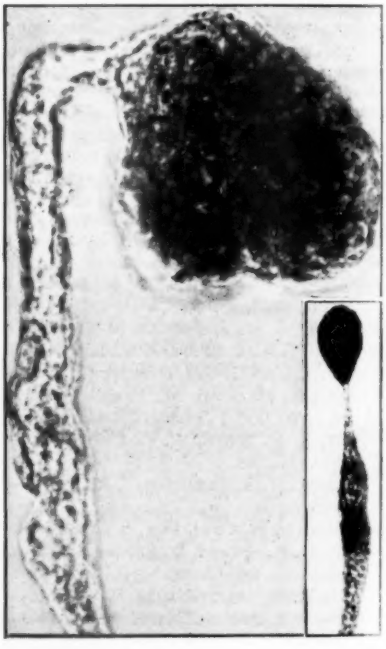

FIG. 2. Inset FIG. 3.

FIG. 1.—Phase contrast × 223. Fanconi syndrome. Shows narrow elongated neck of the proximal tubule seen in Case V.

FIG. 2.—× 307. Fanconi syndrome. Shows phase contrast photomicrograph of glomerulus and proximal tubule of Case VI. Note that the tubule is narrower than normal and that the epithelium is flattened, whilst the lumen is widely dilated.

FIG. 3 (inset).—Phase contrast × 80. Family (T). Note that the proximal tubule shows an absence of convolutions and that the tubule is shorter than normal.

In the second family (T), two male siblings again presented at birth with nephrotic-like syndrome. The parents were not related. Both children died at 4 months and 4½ months respectively. The microdissection of the nephrons showed a slightly different anatomical lesion. Here the proximal tubule was considerably shorter than normal and almost completely devoid of convolutions, in addition the epithelium was flattened and the lumen grossly dilated (Fig. 3). The findings in both these families are to be reported fully elsewhere.

Another syndrome which we have studied extensively is that of acute tubular necrosis. In the past the emphasis has been placed on the lesions of lower nephron and of the tubulo-venous ruptures. In our experience the latter lesion occurs more commonly in the more severe cases, such as crush syndrome. The interesting feature of our study is the focal

nature of the lesion and particularly the changes seen in the proximal tubule. If we trace a nephron through its course we see that in patients dying thirty-six hours after the onset there are areas of increased translucency and that there is a loss of epithelial pattern. At the same time some nephrons appear to escape injury whilst others have extensive focal damage. The focal nature of the lesion is extremely interesting, and is well shown in this phase contrast photograph of the loop of Henle (*see* Fig. 4).

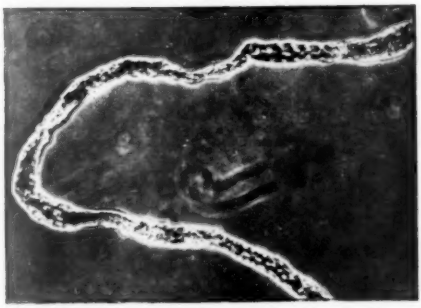

FIG. 4.—Phase contrast × 124. The loop of Henle of a case of acute tubular necrosis dying six days after injury. Note localized areas of epithelial necrosis.

In the early stages many of the glomeruli are engorged with blood, as if stasis of blood has occurred. This raises the possibility that the biochemical changes lower in the nephron may cause some reflex action in the glomerular capillaries. Regeneration of the tubular epithelium is also apparent by this method early in the disease, giving rise later to dilatation of the tubular lumen in some, with extensive overgrowth in others. Such changes are associated in life with extensive electrolyte loss and this has led us to study the kidneys of those who during life have shown excessive urinary electrolyte loss, which we have so far divided into three groups:

(1) Those in which the epithelium of the proximal tubule appears anatomically normal.

(2) Those in which the epithelium shows areas of increased translucency with or without atrophy of the epithelium.

(3) Those in which there is atrophy of the epithelium with elongation and excessive convolutions of the proximal tubule with a reduction in the total number of nephrons.

In the first group we were unable to find any abnormality of the nephron of the kidney of the case described by Cort (1954) and we can only presume that the kidney was responding abnormally to outside influences.

In the second group the findings have already been reported (Darmady *et al.*, 1955).

In the third group the kidneys of a patient described as "salt losing" nephritis were sent to us by Dr. A. A. G. Lewis. Both kidneys were considerably smaller than normal. Dissection showed that the total number of nephrons was very considerably reduced, and that in the remaining nephrons the proximal tubules were greatly elongated, and were of two types. In the first the epithelium was flattened, and the width of the tubules reduced, in the second the proximal tubules were ballooned, the epithelium flattened, and the lumen widely dilated. Both types showed excessive convolutions.

In conclusion, we believe that the microdissection of the nephron is a valuable method for demonstrating the exact site of lesions within the kidney, particularly for small anatomical lesions. Owing to maceration in acid, histochemical methods are not available, nor is it possible to study intracellular details.

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Section of the History of Medicine

President—Sir ZACHARY COPE, M.S., M.D., F.R.C.S.

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The Effects of Epidemics on Population and Social Life

By FFRANGCON ROBERTS, M.D.

THE history of medicine is usually presented in two forms: accounts of the evolution of medical knowledge such as those written by Fielding Garrison and Douglas Guthrie, and discussions on medical philosophy such as have come from the pens of Allbutt, Newman, Singer, Shryock and others. But inspiring as is the story thus told, these accounts leave entirely untouched the effects of medical progress upon population and social life. For, until the scientific era, philosophy was barren of results, while advances, even including the fundamental discovery of the circulation of the blood, were totally without influence upon practice until modern times: and the pathological work of Hunter, the surgery of Pott and the invention of the stethoscope only influenced the treatment of individual patients. Indeed, up to the time of Pasteur and Lister there were only two medical advances which exerted a mass influence. These were the treatment of smallpox by inoculation and vaccination and the revolution in midwifery inaugurated by Smellie. Apart from these, progress consisted entirely in the cult of cleanliness and the development of sanitation, and although the medical profession played a leading part, not until such progress was reinforced by bacteriology can it be said to have become medical in the modern sense of this term.

Throughout the ages population and social life have been determined by two factors, food-production and epidemic disease. This aspect of medical history has unfortunately not received from medical writers the attention which it merits. Information on the subject is to be found, not in medical books, but in the works of economic historians and sociologists. Illuminating accounts are given by Miss M. C. Buer in "Health, Wealth and Population" (London, 1926), and by Mrs. Dorothy George in "London Life in the Eighteenth Century" (3rd edit., London, 1951); and the subject is treated incidentally by Trevelyan and Clapham. Economists whom I have met display a lively interest in vital topics such as the relation between the death-rate and the price of wheat. But while they know more about this aspect of medicine than we do, their lack of first-hand knowledge often leads them into error. Moreover, some sociologists have imparted a political bias to such knowledge as they have picked up, and unfortunately many medical writers have accepted these views without subjecting them to professional criticism. There is a great need for co-operation between members of our profession and the economists, co-operation which this Society might well foster to the advantage of both parties. Here I propose to discuss the effect of epidemics on population, with particular regard to the evolution of medical thought on the subject.

THE ORIGIN OF INFECTIOUS DISEASES

That higher forms of life have always been attacked by bacteria is proved by fossil remains. There are examples of coccal infection dating from the Pre-Cambrian era over 500 million years ago, of osteomyelitis of the spine in reptiles 200 million years ago, and of carious teeth, joint infections and bone necrosis from later periods (Zinsser, 1935). Hecker (1859) wrote: "The remains of animals make us indeed acquainted even now with diseases to which brute creation was subject long ere the waters overflowed, and the mountains sunk." It is, however, widely held that organisms which are now parasitic evolved from organisms which were free-living and saprophytic, a view which Carr-Saunders (1922) has done much to develop. This view has recently been expounded by Hare (1954). He believes that man was not attacked by parasites until he began to live in villages, that is during the neolithic period, 18,000–6,000 B.C. In the previous palæolithic period, which covered 98% of man's total existence, the only parasites were those which man shared with other animals, e.g. tapeworm, bilharzia, staphylococcus and *B. coli*. In support of this view Hare argues that, if all the present parasites had existed then, man could not have survived. Moreover the New World was colonized from the Old, North America from Northern Asia in 12,000 B.C. and Tierra del Fuego about 2,000 B.C. Yet no Old World diseases were found in the New World.

Carr-Saunders, who is concerned to refute the Malthusian doctrine, brings evidence from early travellers and missionaries to show that primitive races such as the Australian Bushmen and the Tasmanians, who correspond to our palæolithic ancestors in their stage of development, were, before contact with white man, long-lived, strong and perfectly free from disease of all kinds, and free also from famine. By infanticide, marriage restrictions

and other tribal customs they had instinctively and intelligently adjusted population to what Cannan called the optimum population. It happens, however, that a similar world-survey was made 150 years earlier by Malthus. The evidence which Malthus collected was the exact opposite; his informants found the natives living in extreme misery and subject to many diseases.

The legend of the healthy savage would be of no more than academic interest were it not that many people have deduced from it that if we undo the evils of civilization we shall re-enter the Golden Age of Health. This argument is suggested by the following passage from the Report of the Royal Commission on Population (1949): "It was only with the coming of the Copper, Bronze and Iron Ages, which brought with them, among other things, successive cataclysms, and higher death-rates from disease and war that an age-old system of regulation of numbers (i.e. infanticide, tribal customs, etc.) was disrupted."

Without, however, subscribing to the legend of the healthy savage we can at least agree with the general thesis that the agglomeration of human beings in communities provided ideal conditions for pathogenic organisms to thrive.

England in the Middle Ages

Between the Domesday Survey, 1089, and the present day the population of England and Wales shows two phases: a phase of extremely slow growth up to 1750 and a phase of extremely rapid growth afterwards. In the 650 years of the first phase population rose from 1,500,000 to only 6,300,000. There were considerable fluctuations, the greatest of course being the Black Death in 1349, when population fell from 3,000,000 to about 2,000,000. The Black Death was, however, by no means the unique event it is sometimes thought to have been. There had been the great epidemic in A.D. 543 in the reign of Justinian. In the seventh century Bede recorded immense depopulation and for the next seven centuries epidemics played havoc almost continuously.

The outstanding feature of society, lasting up to modern times, was the immense child mortality, a fact which is rarely realized. Creighton (1891) expresses surprise that although we have descriptions of the same diseases as those occurring now—cancer, consumption, dropsy, etc.—infant sickness and mortality pass unmentioned. The reason, however, is that these were taken for granted; they were expected and were therefore not worth worrying about. Trevelyan (1942) says: "The death-rate, even in upper class families, was very heavy, and the poor only expected a slender proportion of their immense progeny to survive."

This immense mortality cannot be expressed in figures, but it can be deduced from the almost stationary population which, under the best circumstances, could increase only at an infinitesimal rate as more land was brought into cultivation. Calculation shows that a township of 1,000 inhabitants would take 100 years to increase to 1,200. In each family there was room for only two children to survive; the rest had to die. Biologically such mortality was indispensable for the continuance of the race, a fact noted by Malthus. For had there not been an excess of births in the good times the race could not have survived the bad times.

The Effects of Urbanization

Virulent visitations had always affected the country more or less uniformly except for the seaports. But during the fifteenth century towns became sufficiently large to make them more liable to infection than the rural areas. This to my mind marks an important turning-point. We get a division of the country into the rural areas where births exceeded deaths and the towns where deaths exceeded births, the balance being made up by migration into the towns. Thus began the condition described by Rousseau: "Les villes sont le gouffre de l'espèce humaine." We see the importance of this when we study the so-called Great Plague of London in 1665. Most of us carry from our school days the impression that this event was a bolt from the blue, terminated by the Great Fire in the following year. This is quite misleading. In the first place relatively to population it was not outstanding. Plague had continued off and on ever since the Black Death. Between 1607 and 1665 London was only free from it in four widely separated years. The chief visitations are shown in Table I.

Table I.—Plague in London

Year	Deaths	Population	Year	Deaths	Population
1593	15,000	120,000—150,000 (?)	1640–1647	14,420	
1603	33,347	250,000	1662		384,000
1625	41,313	320,000	1665	97,306	460,000
1636	12,000		1700		674,000
1637	3,082				

What was remarkable about the Great Plague was that it was the last. Why it disappeared remains a mystery. The popular idea that the infection was destroyed by the Great Fire

cannot be accepted. The fire did not involve the parts worst affected, it must have aggravated overcrowding and it was not followed by any improvement in sanitation. Moreover plague came to an end at the same time all over Western Europe except for the Marseilles epidemic in 1720. The modern theory, accepted by Bell (1951), attributes its disappearance to the destruction of the black rat by the Norwegian brown rat, the latter being a much less efficient carrier.

This immense and repeated mortality had no effect whatever on the population of London. John Graunt (1662), who may be called the first medical statistician, stated his belief that however severely London might be affected the population would always recover in two years owing to immigration from the country. Bell writes:

> "The Plague took adult life in large proportion. Infant mortality thereafter kept down the population much as plague had done. So vast was the sacrifice of infant life in London from the Restoration until late in the eighteenth century that the deaths under the age of two years amounted in some years to two-fifths of the deaths at all ages. . . . The London mother could expect the survival of but one-half, or little more than one-half of the family to which she gave birth. Still there was this human sacrifice, not indeed to the Moloch of Plague, but to another of the vexed gods. To man's ignorance Nature is inexorable in extracting the penalty."

This, to my mind, is quite the wrong way to look at it. The truth is that medical science cannot increase the population beyond food-supply. London had in the country a vast reservoir of people on which it could draw. In the country only a limited number could be supported. As Arthur Young wrote of a later period, "Ten times the boasts are sounded in the ears of country fools to induce them to quit their healthy, clean fields for a region of dirt, stink and noise." But the fields, however healthy and clean, could not support more than two children in each family; the rest were compelled to migrate to the towns if they were not to die of starvation. Accounts of the Great Plague are certainly horrifying, but only because people died in such large numbers at once. But those same people would have died of starvation in the country if there had not been London for them to go to.

Disease Substitution

No longer overwhelmed by the devastation caused by plague, doctors had time to interest themselves in other epidemic diseases, notably smallpox which came into prominence in 1602. As to the cause, two opposite views were held. On the one hand there was the strong popular belief in contagion, shown by the insistence on quarantine and the shutting up of houses containing the infected. On the other hand there was the belief in emanations from the earth. Even as late as 1891 Creighton believed in a virus rising from ground contaminated by superficial burials. In Victorian times travellers in the East noted that during epidemics of plague rats behaved oddly. Emerging from their holes they sprang upwards on their hind legs as though trying to jump out of something and then fell down dead. It is interesting to note that quite recently Dalrymple-Champneys (1955), discussing before this Society the mysterious behaviour of epidemics, found it necessary to invoke cosmic influences.

The doctors of the period made up for their ignorance of pathology by the application of statistics under the influence of Graunt, Sir William Petty, Heberden junr., Bissett Hawkins and William Farr, the main problem which interested them being the relation between different diseases and the way in which one disease took the place of another. Haygarth (1793) asserted that "a considerable number of those who now die of the smallpox would die in childhood of other diseases if this distemper were exterminated." This was the very thing Malthus (1789) wanted, for it was a natural corollary to his theory of population. In a famous passage in the *Essay* he says:

> "I feel not the slightest doubt that if the introduction of the cowpox should extirpate the smallpox, and yet the number of marriages continue the same, we shall find a very perceptible difference in the increased mortality of some other diseases. Nothing could prevent this effect but a sudden start in our agriculture."

The same idea was picturesquely expressed by Heberden (1801): "We cannot lower the waters of misery by pressing them down in different places, which must necessarily make them rise somewhere else. . . . Changes in diseases correspond to the alterations in the channels through which the great stream of mortality is constantly flowing."

The disappearance of plague, according to Heberden, was followed by an increase in consumption, paralysis, gout, lunacy and smallpox, due to "idleness, intemperance, covetousness, anxiety and manufactories".

Marshall (1819) wrote: "In Sydenham's time it was computed that sixty-six thousand out of a hundred thousand died in London of fevers. This large proportion of fevers is now supplanted by other diseases; and even our fevers are not of the same complexion that they were in those days, for we are strangers to the symptoms in them denoting their former pestilential and malignant quality."

Bissett Hawkins (1829) noted that with the disappearance of the old diseases others had become more prevalent: scarlet fever, consumption, gout, dropsy and all diseases of brain and nerves. In words which have become familiar to the modern ear he attributed this to "great opulence, less manual labour, more intellectual pursuits, sedentary occupations and multiplication of political interests".

Gilbert Blane (1822) agreed with Malthus "that such a saving of life as is within the reach of vaccination, or any other medical means, can be of little value to the great interests of society". But while he admitted this as a maxim of political science, he opposed to it the greater maxim of moral science. "Social institutions," he said, "and the dependence of individuals upon each other, or the human species in any form, could not exist without kind affection and beneficence, and whatever is amiable and excellent in the human character." Malthus's theory therefore did not absolve doctors from their duty to preserve lives and alleviate suffering.

William Farr and Robert Watt

Among the most violent opponents of Malthus was William Farr who ranged himself whole-heartedly on the side of the optimists, Godwin (Shelley's father-in-law) and Condorcet, that tragic figure who wrote his encomium on optimism though fully aware that he could not escape the guillotine. In his reports from the Register Office Farr made several references to the subject. The means of subsistence, he thought, could always be made to increase faster than the increase of population. The severity of the struggle for existence called forth the excitement of battle and energy and the perpetual selection of finer varieties. Hence England's greatness. "The state of nations at the present day, and the history of past ages, prove that the maintenance of equilibrium between subsistence and population . . . has been left hitherto to the sense of both sexes." This comes very near to Godwin's view: "Strip the commerce of the sexes of all its attendant circumstances and it would be generally despised", a consummation envisaged in a more violent form by George Orwell in "1984".

"The means of regulation", said Farr, "are in the hands of nature and society for increasing and diminishing population and are simple, efficient and quite compatible with our ideas of the divine government of the world. . . . Population demonstrates the safeguards by which human life has been surrounded by God and the laws."

It will thus be seen that, great statistician as Farr certainly was, his excursion into philosophy landed him in a jumble of religion, rationalism, mystique and jingoism. The astonishing thing is that, although knowing better than anyone else the immense child-mortality from infectious disease, he should write in this vein. It seems to have been a curious blind spot in his outlook for which I think there were two reasons. First, he lived in an age of rapid industrial expansion and unbounded optimism, the age of Tennyson and the Great Exhibition. Secondly, this optimism justified an intense religious conviction that all was right with the world; every argument had to demonstrate the goodness of God, confirming the Pauline message: "All things work together for good to them that love God."

But although Farr objected to the doctrine of Malthus, yet (and here again he showed inconsistency) he accepted its logical corollary, the theory of disease-substitution. This was owing to the influence of that remarkable man Robert Watt.

Born in 1774, Robert Watt started life first as a ploughboy, then as a carpenter. Entering Glasgow University he distinguished himself in Greek, and became a schoolmaster. At the age of 24 he learnt medicine in an apothecary's shop and in the following year, having obtained a licence, set up in practice at Paisley. In 1808 he published a book on Diabetes. In 1812 he compiled a catalogue of Medical Books with 1,000 entries; he also formed a museum. In 1814 he published anonymously "Rules of Life with Reflections on the Manners and Disposition of Mankind." He founded the Glasgow Medical Society, becoming its first President. His greatest work, however, was the "Bibliotheca Britannica: A General Index to British and Foreign Literature," a vast undertaking which caused his premature death in 1819.

The book which concerns us here is his "Essay on the Chin Cough and the Relative Mortality of the Principal Diseases of Children" (1813). From a careful examination of the burial registers Watt found that in 1791 Glasgow, with a population of 66,600, had the worst record of any city for smallpox, deaths being 114 in October and 113 in November. In 1808, the population being over 100,000, deaths from smallpox were very few, but deaths from measles rose considerably, being 259 in May and 260 in June, and there was a significant increase in whooping-cough. In thirty years smallpox declined to one-fifth, but measles increased eleven times. The heavy mortality from measles was popularly attributed to smallpox inoculation, but Watt stoutly denied it. In 1659 Thomas Willis had maintained that smallpox fortified children against measles. Watt at first agreed, but later brought forward a different explanation. He found that between 1783 and 1812 deaths of children

under two had decreased, but deaths between five and ten had increased. The transfer to measles was therefore due to the fact that smallpox usually came first and carried off the weakly infants. When we consider the overwhelming power of infectious diseases at a time when half the children died before reaching the age of ten it is clear that the removal of the first hurdle was sufficient to cause a greater number to fall at the second.

Watt's theory met with some opposition particularly from Jenner who objected to what he called its evil tendency, and it seemed to be proved false by a further outbreak of smallpox. Later experience, however, proved its truth, for when smallpox continued to decline, scarlet fever came into prominence, diphtheria appeared in 1858 and cerebrospinal fever in 1865.

These considerations led Farr to write in 1874: "The zymotic diseases replace each other; and when one is rooted out, it is apt to be replaced by others which ravage the human race indifferently whenever the conditions of human life are wanting. They have this property in common with weeds and other forms of life: as one species recedes another advances. . . . For the mere exclusion of one out of many diseases appears to be taken advantage of by those other diseases, just as the extirpation of one weed makes way for other kinds of weeds in a foul garden."

Farr carried the argument further. Following Blane, who, in 1815, had attributed the increase in consumption in young adults to the saving of sickly children, he said that "the effect of the subtraction of the early fatal zymotic diseases and of phthisis, fatal in middle life, is to leave greater numbers alive at the advanced ages—greater numbers to die of the diseases attendant on advancing age". And he made this calculation, pregnant with meaning for the future: "If those who had cholera in Paris had been seized by consumption they would have endured 73,000 years of sickness instead of 158,118 days [i.e. 433 years]; the living in the epidemics of the Middle Ages could not have watched the sick if their diseases had been protracted."

The substitution of chronic for infectious diseases was indeed well under way when Farr wrote, for in Chadwick's tables for the year 1838 deaths from infectious diseases were far surpassed by deaths from diseases due to other causes.

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[*June* 1, 1955]

The Medical Student Through the Ages

By Sir WELDON DALRYMPLE-CHAMPNEYS, Bt., D.M., F.R.C.P.

INTRODUCTION

"THE dissecting-room is his favourite resort for refreshment, and he broils sprats and red herrings on the fire-shovel with consummate skill, amusing himself during the process of his culinary arrangements by sawing the corners off the stone mantelpiece, throwing cinders at the new man, or seeing how long it takes to bore a hole through one of the stools with a red-hot poker." The passage I have just quoted is from a little book entitled "The London Medical Student," by Albert Smith, published in 1861 and sold for one shilling, a book which my father commended to my notice many years since and which suggested to me an investigation of that strange genus, the medical student.

A complete consideration of the medical student through the ages would, of course,

require a lengthy treatise, and not an hour's dissertation and I have, therefore, aimed at giving you a picture, necessarily very incomplete, of the medical student as an individual, his origins, conditions of life, habits, reputation, &c., leaving aside his education, except in so far as it affected these other aspects.

I have searched, so far as I was able, the early records, because, as I sought to show in my Presidential Address to the Section of Epidemiology of this Society in 1944 (Dalrymple-Champneys, 1944) in respect of the fully fledged doctor, it is profitable to mark the changes which have occurred through the ages and their relationship to the state of society at the time and in the country under consideration. These early records are, of course, scanty and deductions from them often speculative, whereas those of the Middle Ages and even more of the last two centuries are far more plentiful, but I shall try to preserve some balance here. In order to shorten this account I have not considered the ancient civilizations beyond the point where rational medicine, whether Greek or its child, Western medicine made its impact.

"Medical Students" among Primitive Races

When considering the equivalent of the medical student in primitive times, or to-day among primitive races, it is necessary to examine briefly the profession for which he was (or is) training. The function of the primitive medical practitioner or witch doctor is through secret traditional lore and by means of his mystical art to counteract enchantments, fend off demons, say how an enraged deity may be pacified, influence the weather, ensure success in the chase or a favourable result in battle, and foretell the future—a comprehensive assignment which not even our National Health Service completely covers. To fulfil this task he employs both physical means, some of which are of genuine efficacy, and psychological methods—chiefly suggestion (Neuburger, 1910). In order to preserve the requisite degree of mystery in their doings such people live apart from the rest of the community and cultivate habits in regard to eating, sleeping and occupation different from the ordinary members of their tribe.

The student witch doctors of some tribes are drawn from the families of the qualified practitioners, in others they are selected for the aptitude shown by them during the training accompanying the initiation at or around puberty (Bolinder, 1954), whilst among yet other peoples their selection depends on the circumstances of their birth (e.g. being one of twins) their liability to dreaming, or to epileptiform attacks (e.g. the Shamans of the native Siberian races). The candidates thus chosen undergo a period of hard and solitary training, either at the hands of old practitioners chosen for the purpose by the association of witch doctors, where such exists, or by an individual medicine man to whom the student has attached himself. In many tribes the candidate is only accepted as a regular practitioner if he can pass a practical examination. And here I would pause for a moment to remark that though the rewards of the practitioner are often considerable enough to furnish a powerful inducement to youths to enter this profession, yet the profession carries with it special risks and the death of a patient cannot always be successfully shifted on to the shoulders of the "malevolent medicine man of an unfriendly tribe".

Mesopotamia

Mesopotamia, which has been called the cradle of civilization, already exhibits as early as about 4,000 B.C. an important change in the character of its doctors, namely their identification with the priesthood, a character which persists through all subsequent civilizations (with the possible exception of the Egyptian in its early phases) until the late Middle Ages. Though we are dealing here, even in Sumerian times, with a much more advanced and elaborate civilization than that of the primitive peoples to which I have just referred, yet medicine is still largely magic and the principal science conditioning it is that of mathematics. As Neuburger says, "theory was deduced from experience, and facts acquired empirically were systematized from the point of view of a demonistic religion coloured by astrology". The influence of numbers was held to be of great importance, especially the number 7 which was considered very malignant, so the Mesopotamian priests can perhaps be regarded as the true ancestors of our modern statisticians! The great complication of their medico-astrological system as well as the severe penalties for unsuccessful treatment laid down in the famous code of Hammurabi (*c.* 2,200 B.C.) suggest that the medical student of the time must have undergone a long and intricate training before he could stand much chance of survival in the world of medical practice. Thus the code lays down that "If the physician make a severe wound with the bronze operating knife and the patient die, or if he open the groin with a bronze operating knife and the patient lose his eye, he shall have his hands cut off". If the patient were a slave the physician merely had to replace him by another slave. It is worth noting that the doctor was only controlled by regulations such as this when acting as a *surgeon*, but as regards *medical* treatment he appears to have enjoyed immunity from the law as a member of the priestly caste (Contenau, 1938).

Egypt

In speaking of the ancient Mesopotamian civilizations and the priestly character of their physicians I have mentioned that there was a possible exception to the universality of this custom in one civilization, namely in the earlier dynasties of Egypt. According to Withington (1894), during the fifth dynasty (*c.* 3,500 B.C.) and perhaps earlier, when life in Egypt had a more patriarchal character, physicians and other professional men had not yet been absorbed into the priesthood and their tutelar deity was still Sekhet, the lion-headed Goddess of War, and not Thoth, the God of Wisdom, as in later times. Moreover, the hieroglyph representing the physician was a lancet and cupping horn, but later this disappeared. However, little is known about the doctor or medical student of this early period and by the time the evidence becomes more plentiful we find the medical student studying alongside the budding judges, astronomers, mathematicians and others in the schools associated with the temples, and living in the houses attached to the schools under the inspection and discipline of their teachers, one of whom in a passage translated by Chabas thus admonishes his pupil: "Let not idleness overtake thee else shalt thou be severely chastised. Hang not thine affections upon pleasures and take care that the books fall not from thine hand. Exercise thyself in conversation and speak with thy superiors in learning. When thou shalt grow older thou wilt recognize how important this is: whoso is dextrous in his craft achieves power and fame." Another frivolous student is thus reproved: "It has been reported to me that thou neglectest thy studies and seekest only thy pleasure, wandering from tavern to tavern. But what profiteth the odour of beer? Avoid it, for it drives people away from thee, impoverishes thy wits, and likens thee to a broken oar upon the deck of a ship." These medical students were drawn from all classes, industry and talent being the only passports to the schools. It seems almost certain that, apart from textbooks (the 42 sacred books and probably commentaries on them), the student received practical instruction in the examination and treatment of the patients who came to the temples for healing. I must not close this brief reference to the subjects which the medical student of ancient Egypt had to study without referring to hygiene, which was so highly developed there and had such a profound influence on the whole life of the people and on that of succeeding civilizations such as the Jewish and the Greek. Herodotus says that "the Egyptians are, with the Libyans, the healthiest nation" and Diodorus remarks that "the whole manner of life was so evenly ordered that it would appear as though it had been arranged according to the rules of health by a learned physician, rather than by a lawgiver". In this subject the medical student seems, therefore, to have been instructed from a body of learning based on experience and not on magical theories, and consequently far more advanced than the knowledge of curative medicine, so far as we can tell from records at present available.

Persia

Though little is known of medical education or practice in ancient Persia a passing reference must be made to the practical test to which a budding surgeon was subjected (the surgeon being the lowest of the three grades of medical practitioner). This test consisted of two parts, the first carried out on three "heretics", and if all three died following their operations then the surgeon was debarred from practice for the rest of his life. If he passed this first part of the test he proceeded to the second part consisting of operations on three "believers", and if all three survived then he was qualified for life, however many patients he might kill subsequently.

India

Medicine in India in the first or Vedic period (up to about 800 B.C.) consisted in an attempt to fit empirical knowledge into a framework of polytheism and a demonistic conception of nature, but I have not been able to obtain any information regarding the recruitment and training of medical practitioners. When we come to the Brahmanic period, the golden age of Indian medicine, there are several interesting features related to my subject. The true medical practitioners belonged to the high mixed class of Ambastha, descended on the father's side from Brahmans, but they were assisted by a subordinate type of practitioner, empiricists, belonging to the lower caste of the Vaisya. The Ambastha physicians were undoubtedly priestly, they were chosen from good families, preferably medical ones, and manual dexterity and certain physical and moral endowments were required of the candidates for instruction. Their training closely resembled that of Brahman scholars and emphasized reverence for Brahmans, their teachers and their ancestors. The youths were admitted in winter with a waxing moon, upon an auspicious day, and in the presence of the Brahmans. At a ceremony of dedication they took a vow to observe their religious duties and the rules of their profession. Their instruction, which lasted six years, was partly theoretical, consisting mostly of learning by heart precepts explained by the teacher and derived from an approved textbook, and partly practical instruction given at the bedside, and in the practice

of surgical procedures. One admirable feature was the rule that no teacher might instruct more than from four to six pupils at the same time. At the end of the course they had to obtain leave to practise from the king. As regards medical ethics, in contrast to the oft-quoted saying "In illness the physician is a father, in convalescence a friend; when health is restored a guardian", the practitioner was forbidden to treat incurables, hunters, fowlers, caste-breakers and criminals, a prohibition which we find with local variations in the medical codes of all civilizations (including the Hippocratic code) before the Christian era.

China

In ancient China, as in all early civilizations, medicine was practised by the sorcerer or priest, often referred to as the "priest-doctor" (Wu I). The powers of these men were unlimited and their influence extended to every walk of life then extant (Wong and Wu, 1936). The functions of priest and doctor were not separated till the Chou dynasty in 1140 B.C. and the Chou Li, a classic of this period, directs the sorcerer to make offerings in time of drought and the doctor to superintend all matters relating to medicine and to collect medicinal herbs. The superstition of the masses, however, made such a separation largely ineffective in practice, which provoked the celebrated Pien Ch'iao to remark that "A case is incurable if one believes in sorcerers instead of in doctors"—an aphorism which has its applications even to-day! All the same whether practised by sorcerers or doctors medicine in those early times was, with all its limitations, based upon observation and knowledge, whereas when we come to the middle of the Chou dynasty, about 722 B.C., the age of Confucius, Lao Tzu and Mencius and one of the most glorious periods in Chinese history, this empirical art had become replaced by an elaborate theoretical system of ever-growing complexity and diminishing meaning and effectiveness. In contrast to the content of medicine, medical organization was highly developed during this period and the Chou Rituals distinguish four kinds of doctors, namely, physicians, surgeons, dietitians and veterinarians. The work of all these doctors was to be examined at the end of the year by the chief doctor and their salaries fixed according to the success of their treatments—shall we come to that one day? Medical students, like other students, were members of the scholar-gentry, the mandarinate into which, Dr. J. Needham tells me, families rose and out of which they sank within a few generations. These students generally had some Taoist affiliations, but the profession was not greatly looked down on by Confucian scholars, some of whom certainly practised medicine. In later centuries Buddhist compassion must, he thinks, certainly have provided a considerable urge to join the profession and no abbey, whether Taoist or Buddhist, was probably ever without its medical specialists. Medical education was first started in the T'ang dynasty (A.D. 618–906) and in the Northern Sung dynasty (A.D. 960–1126) regular medical schools were organized, first in the capital and later in other parts of the country, starting with the foundation of an Imperial Medical College in A.D. 1076. These colleges had their ups and downs and many were closed down at certain periods, often to be reopened later. An elaborate system of examinations, both oral and clinical, was a feature of this educational system and lists of textbooks recommended to the students are still extant. The teachers were liable to punishment or dismissal not only for neglecting their teaching but also for failure to make their students work. State examinations fell into disuse at one period, but were revived under the Yuan dynasty in A.D. 1317 and successful candidates were guaranteed posts, the importance of which depended on the quality of their performance at the examinations. It is worth noting that during the same dynasty women doctors were first given recognition and special arrangements made for their examination.

Chinese medicine began to decline under the Ming dynasty (1368–1644), reaching its lowest ebb in the Ch'ing period (1644–1911). All medical colleges disappeared with the exception of the Imperial College of Physicians in Peking, whose sole function was to train physicians for the imperial family, so that the ordinary physicians had no opportunity of preparing for their life's work, nor was there any kind of government supervision or code of ethics. The higher grades of doctor served an apprenticeship under an old doctor or in a druggist's shop and the public placed most confidence in members of medical families, the longer the tradition the higher the prestige (Morgan, 1922-23).

Jewry

The sources of information with regard to Jewish doctors and medical students especially in pre-Talmudic times (before the third century A.D.) are very scanty, as no medical works have come down to us from the ancient Hebrews. One must also remember, as Dr. Charles Singer has pointed out to me, that the Jews being an agricultural race with scattered population and poor communications, the conditions for the development of a real medical profession were mostly absent. However, true doctors eventually appeared, and during the Talmudic period medicine was an officially recognized profession. These doctors were definitely general practitioners and not priests (Friedenwald, 1944), the latter's medical

functions being confined to the practice of preventive medicine by the enforcement of public health ordinances, though there were rabbis such as Samuel (A.D. 200) who possessed medical knowledge and applied it (Snowman, 1935). Moreover, all judges were supposed to have medical knowledge and even knowledge of pathology to enable them to decide whether meat was fit for human consumption. Medical ethics in Jewry were certainly greatly in advance of those elsewhere, even in classical Greece, for, as Preuss points out (Preuss, 1923), the Jewish physician was not an authorized killer, nor did Jewish law punish him by death or mutilation if his patient died, nor was he forbidden, as in the Hippocratic code, to treat apparently hopeless cases. These conditions and the fact that the patient was enjoined by his religion to pay the doctor his due fees, sometimes demanded in advance, must have made the profession seem not unattractive to the prospective medical student. According to Snowman nothing is known about the methods of medical education, beyond the indication that physicians took private pupils, but W. Pagel (private communication, 1955) considers that the frequent references to visits by "physicians" (in the plural) means that the real physician was accompanied by his pupils, for instance the physician Thodos "and all physicians with him" repair to the academy at Lydda in order to decide whether certain bones belonged to the same skeleton.

Greece

In contrast to the magical and rigidly traditional world of Assyrian medicine, and the more rational but hardly less rigid Egyptian cult, the medicine of ancient Greece, whose flower is preserved for us in the Hippocratic writings, seems like a breath of fresh air or a flooding of sunshine into a dank and sinister cave, for though the priests of the temples of Asklepios jealously guarded the belief in divine revelation as a guide to medical treatment, yet they were content to maintain the closest and most friendly relations with the true doctors, the Asklepiadae whose medical schools were established in close proximity to the temples which they regularly frequented and where they studied the illnesses and cures of patients treated there for all kinds of diseases.

Medical teaching in these schools of the Asklepiadae—which resembled modern academies rather than universities—began at an early age and in the common case of a doctor's son was naturally initiated by the father. It was continued by practical training from other doctors to whom an honorarium was payable and the pupil when qualified was bound to teach the healing art to the sons of his teacher without remuneration (Puschmann, 1891). The oath which the student eventually took on admission to the Society of the Asklepiadae is preserved in the later Hippocratic collection and represents a far higher ethical code for the regulation of the doctor's life and practice than the world had known previously. The picture it paints of the relations between teacher and student is one that any teacher to-day might envy, as the budding doctor swore "To regard my teacher in this art as equal to my parents". It is obvious from this oath and from what we know of the way of life in Hippocratic and post-Hippocratic times that the medical student must have lived a far healthier life than in most other ages and countries, and a much more interesting one as Greek medicine, like all Greek learning, derived its glory from the impulse of intense curiosity which alone can further the advancement of scientific research. As time went on this healthy empiricism was gradually stifled and distorted by the influence of religious cults from the East, but enough survived to blossom many centuries later in the Renaissance.

Rome

In the earlier days of Rome of which we have records medical knowledge was transmitted from father to son, or to a relative or friend. Teaching was under the personal supervision of the doctor. Later when Greek medicine came to Rome the Greek doctors taught their art there, and in Rome, as in Greece, medicine was a profession open to anyone who thought he had the necessary ability for it. There were no legal regulations and the medical student obtained his knowledge where and how he liked, so that there was great variation in the quality of the practitioners. Pliny condemned this state of affairs in no uncertain terms, and Galen wrote a treatise on the need for a doctor to be trained in both mind and morals. In Cato's time general education included, with law, military science and agriculture, some knowledge of medicine. The period of medical study varied widely. Galen devoted eleven years to his medical studies, whilst the notorious charlatan Thessalus obtained large numbers of pupils by promising to turn them into doctors in six months. According to Galen many of these pupils could not read or speak correctly. There was, of course, no real anatomical teaching at this time, and even Galen derived most of his anatomical knowledge, as he admits himself, from dissection of the lower animals.

Serious students of medicine learnt chiefly by accompanying their teachers to the homes of the patients and it is not surprising that the visit of a doctor accompanied by a large body of pupils (sometimes 30 or more) was not always appreciated by the patient, as is

shown by Martial's epigram on his doctor Symmachus: "I was ill. Thou camest forthwith to me—accompanied by 100 pupils: 100 ice-cold hands were laid on my body. Till then I had no fever: now I have." Galen tells his pupils to be quiet when entering the sick room, to be clean and attend to their hair; they must not eat onions or garlic before visiting a patient, or drink too much wine, lest they annoy the sufferer by the offensive odour from their mouths and "stink like goats" (Puschmann, 1891).

The Arabs

Few phenomena in history are more curious than the destruction of highly advanced Western civilization by the Arabs, their wise and providential preservation of so much priceless literature taken from their fallen foes, their perpetuation and development up to a certain point of many of the most enlightened ideas of the Greek and Roman writers, and their ultimate failure to progress further on account of their exaggerated respect for tradition. This respect for tradition was not, however, accompanied by a rigid discipline in the classroom; and in the earlier period of Islam, at any rate, the pupils attending the teachers in the mosques (the lectures, by the way, being gratuitous and open to all without distinction of nationality) were encouraged to discuss their teachers' propositions with great freedom. Such lectures were attended by persons of all ages and often from places far away. Such free interchange of knowledge was, of course, encouraged by the fact that Arabic was the common language of all Islamic countries. The students were often given certificates of attendance at their teacher's lectures and a permit to disseminate the knowledge they had acquired from him.

In the later phases of Arabian learning institutions were founded closely resembling universities, such as the "House of Wisdom" founded by the Caliph Hakim Biimrillah at Cairo in 1105, where medicine was taught in conjunction with other sciences and even Jews and Christians were allowed to attend the lectures. At this period the three courses of training open to a medical student were instruction under the personal supervision of a senior physician, attendance at a medical teaching establishment, or finally teaching in one of the many medical schools attached to hospitals.

The doctors of Islam enjoyed high social standing and were often loaded with honours and distinctions, not a few attaining the rank of Vizier, corresponding roughly to a Privy Councillor.

Middle Ages

When we come to the Middle Ages the material available is almost embarassingly plentiful, though there are many questions to which I have not yet found an answer.

First of all it is necessary to emphasize the common background of all mediæval students, to whatever faculty they belonged, and secondly what a very special section of society they represented. The most important prerequisite for any student was, of course, a knowledge of Latin, without which he could derive no benefit from instruction at any university. Latin, as Rashdall (1895) remarks, "was not merely the language of the lecture-room, but theoretically at least of ordinary student life". It was necessary for ordinary intercourse because, at any rate in the earlier period, students from different provinces of the same country could hardly understand each other in their mother tongue and the student bodies of all universities were still very cosmopolitan. It is worth noting that the use of Latin as a lingua franca was made easier by the fact that Englishmen then pronounced Latin in the continental way, the barbarous "English" pronunciation being introduced only in the lifetime of Dr. Caius. At Paris in order to be admitted to studentship a petitioner had to state his case before the Rector in Latin without any interposition of French words. In the later period Latin speaking in College and Hall was strictly enforced by statute—in my time at Oriel we were sconced for quoting Latin or Greek in Hall! The task of teaching Latin to the prospective student was carried out by the Grammar Schools which were widely diffused all over England at this period, whilst in the university towns there were grammar schools of an inferior kind, usually under the control of the university. The university student, including the medical student, was an ecclesiastic, but knowledge of Latin was not confined to the clergy, as even the bailiff of a manor always kept his accounts in Latin.

But let us look back to see where these students came from. The vast majority were of an intermediate social position, sons of knights, yeomen, merchants, tradesmen or thrifty artisans, nephews of successful clerics or promising lads who had attracted the notice of a neighbouring Abbot or Archdeacon. Though the majority were not in really straitened circumstances there are many accounts preserved which illustrate the poverty of some of the students and the begging by which alone they could sustain themselves. Thus a poor student at Bologna in the fifteenth century complained: "The time I should spend at lectures and in study I am driven to waste in begging from door to door, crying scores and scores of times—'Charity, charity, dear masters', and getting the answer 'Begone, and God be with

you'. I appeal both to ecclesiastics and laymen, and am mostly driven from the door, or perchance one may say 'Wait a bit', when I get a dirty scrap of bread which a dog would reject, or I may get fusty beans, bits of skin or gristle, or sour wine" (Allbutt, 1921). As regards age the freshman ranged between 13 and 16 and though it seems certain that boys matured earlier in the circumstances of mediæval life, yet the youth of the students was presumably partly accountable for the wild pranks so common in the universities of the time and the kind of punishment considered appropriate in such cases. In the first part of the period corporal punishment was prescribed for many offences committed by the younger students and at the Sorbonne each Master was responsible for flogging his own clerk when necessary, but at the English Universities the age of whipping was prolonged to the verge of manhood, though in the second half of the fourteenth century the statutes of Queen's College, Oxford, limit it to the "poor boys", who could not pay a fine and whose careers would have been permanently ruined by being sent down. By the beginning of the sixteenth century, however, we find the Brasenose undergraduate reduced to the schoolboy level and whipped by his college lecturer for unprepared lessons, playing, laughing or talking in lecture, making odious comparisons, speaking English, disobeying the Lecturer, not attending at Chapel, &c. Here are a few examples of the wild pranks of the mediæval undergraduate. Gangs of students often strolled the streets at night in any of the university towns, singing, shouting, dancing, beating up the watch, and not infrequently killing citizens who incurred their displeasure, whilst occasionally on the Continent pitched battles ensued between armed students and the retainers of some great lord, lay or ecclesiastic, such as the famous affair between the Paris scholars and the monks of the Abbey of St. Germain in 1278, and the Affaire Savoisy in 1404, in which the retainers of the King of France's Chamberlain, Charles of Savoisy, pursued Paris students of a later generation even into a church where Mass was being celebrated. When it is realized that the student was protected from punishment for even the most outrageous offences including murder by his clerical status, it is no wonder that feeling between town and gown was strong and that the lay population opposed these privileges with bitterness and fury. Only occasionally was the offending student obliged to seek sanctuary as a first step to leaving the country. No doubt this state of things was partly accounted for by the intolerable tedium of student life, from which all amusements in our sense of the word were completely absent, and to the drinking habits of an age which knew neither tea, coffee nor tobacco and in which all important events were celebrated by bibulous feasts. In the Halls or Colleges often the only fire, in winters far more severe than those to which we are accustomed, was in the kitchen and often there was a special statute forbidding students to repair to this sole source of warmth after dinner. The windows of their rooms were closed by wooden shutters, there being no glass windows until about the mid-fifteenth century, the floors were of clay or tiled, bare or strewn with rushes, and the ceiling unplastered. The furniture, except in the case of the few rich students or some of the seniors, consisted of a truckle bed, a table and a few chairs or "playne joyned stooles". Simple bedclothes, which in the case of the humbler scholars did not include sheets, a coffer for his clothes, and a press if he was studious, completed the furnishing of his room.

And what about food? The principal items in the student's diet seem to have been meat, bread, butter and cheese, probably in sufficient quantities, washed down with plenty of small beer. The two main meals were dinner at 10 a.m. (later at 11 a.m.) and supper at 5. The "jentaculum" or early breakfast did not become a regular institution until the fifteenth or sixteenth century and was even then regarded as an extra which the hardier or more economical student would dispense with. This is the more remarkable when one remembers that lectures usually started at 5 a.m. or 6 a.m. in the summer and 7 a.m. in the winter and were held, or course, in unheated rooms. In the earlier period there seems to have been a maximum of three compulsory lectures a day, the first morning lecture sometimes lasting for a prescribed period of three hours, but these were supplemented more and more as time went on by smaller and more informal exercises in Hall or College. The teaching of anatomy when not purely didactic generally consisted in occasional public dissections conducted in a manner which throws an interesting light on the tastes and manners of the Middle Ages. Felix Platter, a medical student of Montpellier in the sixteenth century, describing such a public dissection at which Dr. Guichard, a member of the faculty, presided, but which was actually performed by a barber, as was usual, says that "besides the students, there were in the audience many members of the nobility and bourgeoisie, and even young ladies, in spite of the fact that the subject was a man. There were even some monks" (Vaultier, 1954). But the students at Montpellier obviously found such instruction insufficient because Platter and his friends thought it worth while to hire a house in a secluded neighbourhood to which they brought newly buried bodies which they had snatched from the town's cemeteries at night, an activity which sometimes involved them in armed battles with the monks.

I must not leave this account of the mediæval student without brief reference to a very important condition affecting his life, namely the extraordinary degree of autonomy which

he enjoyed, all the more extraordinary in view of his tender age. This autonomy was greatest in the Italian universities such as those of Padua and Bologna which were governed almost entirely by the student body, the teacher at Bologna, for instance, being obliged to take the oath of obedience to his pupils, without which he was unable to collect his lecture fees and was liable to further punishment at the will of the Rector, an official elected by the student body (Riesman, 1936). In the early period the population of the universities was a very floating one, for not only did students wander from one university to another, but on occasions a large section migrated to another university, or even set up a new university in another town. Thus there was a large migration from Padua to Vercelli in 1228, and from Vicenza to Bologna a little later, and in 1229 when there was a revolt by the University of Paris against the town the King of England invited the University to migrate to his country, a threat which, as usual, brought the town to their knees. At the University of Paris, and at Oxford and Cambridge which were modelled on it, control was in the hands of the Masters and of the Church, the balance of power swaying backwards and forwards, but even here the student had full liberty (unless his parents were rich and made special provision for him) to choose the Master whose lectures he would attend and the Hall where he would live, unless he found his own lodgings in the town. The mediæval Hall was hired by a party of students banding together and the Principal was merely the student who made himself responsible for the rent. Later at Oxford and Cambridge the Chancellor gradually acquired more control over the Halls and the system was gradually superseded on the advent of the Colleges.

Seventeenth Century

An interesting light on the student's life in the seventeenth century is thrown by Pousson (1931) in his account of medical instruction in the University of Bordeaux before the Revolution. From the foundation of this university up to the middle of the sixteenth century the medical students were clerics living in monastic houses under the strictest discipline, their only recreation being to take part in religious processions and pageants. But from that time onwards the students mixed with the population of the town and by their superior education exerted a civilizing influence on the shopkeepers, artisans and small merchants with whom they lodged, as well as by the masques, morality plays, allegories and farces in the French or Gascon languages which they composed themselves and which were within the understanding of the townspeople in general. There were, nevertheless, many less admirable students who, as elsewhere, frequented taverns, started brawls and sometimes killed other students belonging to groups from different regions, or even peaceful townsmen.

As regards the budding barber surgeon at this period his apprenticeship was no life of luxury, as we learn from the autobiography of Johann Dietz whose apprenticeship started at the age of 14 and whose morning meal consisted of a slice of dry bread washed down with water or small beer. At first his duties included carrying logs and water for the maid in the kitchen and carting dung in the garden and punishment was never far off, so that he used to twist the whip up in a towel so that he could escape before it could be untwisted (Dietz, 1915).

It has been commonly supposed that doctors in France before the Revolution were recruited mainly from the upper classes, but Fauvelle (1899) has pointed out that on the contrary they came chiefly from the prosperous bourgeoisie, prosperous because the length of the medical curriculum and the long unremunerative stage succeeding qualification necessitated the possession of some fortune by the student's parents, unless he was lucky enough to have secured the patronage of some rich person. Most medical students of the period had, in fact, great difficulty in making both ends meet. They lived in very simple and often sordid lodgings, but the luckier ones managed to secure a room in a respectable house furnished usually with a bed, a plain wooden table, a chair or stool and an untidy mass of papers, exercise books, theses, &c., besides a few essential textbooks such as Latin translations of Galen and Hippocrates. Their dress in the earlier part of the seventeenth century consisted of black woollen stockings held up by knotted garters, baggy long black boots, the tops of which were fastened by laces to the "pourpoint" or tunic. Over all this the student wore a padded "rabat" or short coat. He wore his own hair, for it was not until the end of the century that wigs came into fashion, together with lace, ribbons, &c. (Cabanès, 1913). The medical course at the University of Paris at this time lasted four years, though doctors' sons and some other privileged persons had this period reduced to twenty-eight months. It is worth noting that anatomical dissection, which was compulsory, was carried out during the first year of study.

Eighteenth Century

The difficulties of obtaining subjects for dissection persisted through the eighteenth century and led at times to scandalous scenes, the toleration of which is a good index of the coarseness of the times. When Dr. Frank Nicholls, later the leading anatomical teacher in England

and one who influenced Hunter, was lecturing at Oxford in 1730, a near riot occurred over a body wanted for dissection. "Hanged at Oxford, one Richard Fuller of Caversham in Oxfordshire, a young man of 26 years of age for murdering his wife. There was sad work on that occasion, the scholars endeavouring to get the dead body, assisted by some Townsmen, and others on the contrary hindering. The relations had provided a coffin to have it decently buried at Caversham but the scholars broke it all to pieces, the body being in it; after which those opposite to the scholars had it again and so for several times, sometimes one side had it and sometimes the other, but the Proctors favouring the relatives, the body was at last delivered to them and brought to the Castle; about eleven at night when all was thought still, it was taken to the water side to send it away in a boat, but to their surprise the scholars were lying in ambush and coffin and all was thrown into the water, but the scholars soon went in in great numbers and drew it out and carried it to Christ Church to dissect it. The tumult was so extraordinary that the town clerk was forced to read the Proclamation but to no purpose, the rioters crying out they did not hear it" (Sinclair and Robb-Smith, 1950).

Nineteenth Century

The system of medical apprenticeship persisted well into the nineteenth century and its conditions at the beginning of this century are described by Jesse S. Myer (1939) in the following passage. "Living under the same roof, as was customary in the days of medical apprenticeship, the preceptor could look after both mind and morals of his pupil. The fledgling, in return for the instruction received at the hands of his master, not only compensated him for his trouble, but performed many of the menial offices of a servant about the house and the office. It was he who prepared the powders, mixed concoctions, made the pills, swept the office, kept the bottles clean, assisted in operations, and often through main force supplied the place of the anæsthetic of to-day in the amputation of limbs and other surgical procedures. He rode about with the doctor from house to house, profiting by his personal experience and jotting down in the pages of his notebook and on the tablets of his memory the words of wisdom that fell from his master's lips." Opportunities for dissection were mostly limited to occasional amputated limbs, but some apprentices were lucky enough to have enlightened masters who took an interest in their pupils' education or had the opportunity of attending classes on anatomy given by local surgeons, as Sir James Paget describes in his autobiography, and, of course, many, like him, went on to a hospital to continue their studies, though at St. Bartholomew's Hospital in 1834 "There was", he says, "very little, or no, personal guidance; the demonstrators had some private pupils, who they 'ground' for the college examinations . . .; the surgeons had apprentices, to whom they seldom taught more than to other students, for the most part the students guided themselves or one another to evil or to good, to various degrees of work or of idleness. No one was in any sense responsible for them".

One important change which took place mainly in this century was the increasing age at which medical education, and indeed university education of all kinds, was started. This change naturally affected both the customs of the students and the kind of discipline necessary to restrain and guide them. But in the United States an opposite movement took place at the end of this period, for Schussler (1928) tells us that at the very beginning of the twentieth century (and presumably at the end of the nineteenth) the medical students at the University of Minnesota were for the most part men who had already been pursuing other occupations for some years and many were fathers with families nearly or quite as old as the freshman of 1928. Many of these mature students still pursued their former occupations in a sporadic manner whilst studying medicine in order to pay their way, just as the American student of to-day often works his way through medical school.

As regards the 1830s, I shall make only passing reference to Dickens' Bob Sawyer and Ben Allen, not only because these famous characters are so well known, but also because their background and even their probable medical schools and haunts have been so vividly painted by my old friend Mr. T. B. Layton (1936). It will be obvious from my opening quotation that even by 1861 their kind had not greatly changed except in appearance. They were still very rough diamonds, living in rather sordid conditions, drinking far too much beer and brandy, fond of practical jokes and coarse humour, still subject to very little supervision or guidance—a mixed lot, as always, comprising all gradations from the waster to the man with a mission. Listen again for a moment to Albert Smith's description of the "grinder" or crammer struggling with his unruly class. " 'What would you do if you were sent for to a person poisoned by oxalic acid' asks the grinder. 'Give him some chalk' returns Mr. Rapp. 'But suppose you had not got any chalk in the house, what would you substitute?' 'Oh anything; soapsuds and pipeclay, old images or cheap confectionery.' 'Yes, that's all very right; but we will presume you could not get any soapsuds and pipeclay, old images or cheap confectionery; in fact, that there was nothing to be found about the

place. What would you do then?' Mr. Manhug cries out from the bottom of the table, 'Let him die and be d———!' 'Now, Mr. Manhug, I really must entreat of you to be more steady' interrupts the Professor. 'You would scrape the ceiling with the fire-shovel, would you not? Plaster contains lime, and lime is an antidote. Recollect that, if you please. They like you to say you would scrape the ceiling, at the Hall: they think it shows a ready invention in emergency. Mr. Newcome, you have heard the last question and answer?' 'Yes, sir' says the fresh arrival, as he finishes making a note of it. . . . 'Well; you are sent for to a man who has hung himself. What would be your first endeavour?' 'To scrape the ceiling with the fire-shovel' mildly observes Mr. Newcome"———and so on. I have no time to conduct you, with the help of the author, through all the metamorphosis of the London medical student, from the new man who "evinces an affection for cloth boots, or short Wellingtons with double soles, and toes shaped like a toad's mouth"; to the instructed student awaiting the awful ordeal of the examination at the Hall "His brain is as full of temporary information as a bad egg is of sulphuretted hydrogen, or a Putney omnibus of damp travellers on a wet day"; and finally to the man who has passed, consuming his "pot of Hospital Medoc" at the adjoining pub, till he and his companions in success finally "run about the streets, crowing like cocks, braying like donkeys, and indulging in the usual buoyant recreations that innocent and happy minds so situated delight to follow".

"Such were the youths who trod our path before.
A path most perilous in ancient times,
Struggling hard to learn Hygeia's lore
Through many ages and in different climes
Yet one with us, seeking a common goal.
What if their motives, to the critic's eyes,
Sometimes seem doubtful. Could we see the soul
Of every doctor then this dark surmise
Might well dissolve, and there beneath reveal
The light from Heaven, so oft unrecognised
From modesty or ignorance, yet real
And above all, by the wise doctor, prized.
For these young neophytes, though raw and wild
Yet had the stuff in them that brings
Peace to the mother of the wailing child
Courage to those afraid to spread their wings
Snatching the body from the brink of death
Changing the desperate gasp to quiet breath."

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United Services Section

President—Sir LIONEL WHITBY, C.V.O., M.C., M.D., F.R.C.P.

[*March* 3, 1955]

The Use and Abuse of the Hospital Laboratory in the Armed Forces

By Group Captain W. P. STAMM, M.B., B.S., M.R.C.P., D.C.P., D.T.M. & H.

A generation ago pathology and morbid anatomy were almost synonymous. It was generally regarded as the dead-end branch of medicine and the pathologist as a morbid mortician showing a ghoulish glee in demonstrating the clinicians' mistakes in the autopsy room; a pastime hardly conducive to amicable co-operation, but which unfortunately survives at times even now.

Since then we have seen great advances in all branches of medicine, nearly every one of which has been made practicable by new or improved laboratory methods. To quote a few examples: the advances made in hæmatological diagnosis and in transfusion technique have all been conceived and developed in the laboratory; the intelligent use of antibiotics depends on bacteriological diagnosis and control of therapy; and the greater use of intravenous electrolytes can only be achieved in a manner likely to benefit the patient when adequate laboratory facilities are available.

These advances have caused a complete change in the clinical importance of pathology: in fact, from being 80% of little more than academic or epidemiological value, hospital pathology has become in the last fifteen years an essential part of medicine's diagnostic and therapeutic machinery, on the accuracy of which the patient's life may depend.

Parallel with this essential growth of hospital pathology, the laboratories have been increasingly burdened with unnecessary routine tests. The tendency to use the laboratory as a diagnostic sieve or slot-machine seems to have originated largely from the innate laziness of mankind, in that it is easier to fill in a form than to examine a patient; partly as a sort of clinicians' insurance policy; and partly from the belief of many clinicians, and even some pathologists, that pathology is an exact science, a misconception which makes some clinicians give more weight to a typewritten report than to the evidence conveyed by their own senses.

If proper use is to be made of the available laboratory resources it is essential that clinicians and pathologists should have a clear idea of the value and limitations of the various tests and should co-operate to improve the standard of accuracy attained.

This is particularly important in the Armed Forces for two reasons: we are dealing with a population initially fit and thereafter under constant medical supervision, so that patients reach hospital with minimal pathological changes; and small variations from normal may be of great significance because of liability to exposure to environmental or physical stress, e.g. early diabetes mellitus in aircrew.

I am, therefore, going to consider briefly the main sources of inaccuracy and error in laboratory work and then suggest how we should work for improvement.

Belk and Sunderman (1947) published a survey in which two samples of citrated blood for hæmoglobin, and aqueous solutions of various other substances, were sent for estimation to 59 Pennsylvania laboratories. The results are shown in Figs. 1, 2, 3 and 4.

Belk and Sunderman were surprised at the wide scatter of the results and considered them below any reasonable standard. The pathologists were aware that they were dealing with test samples so that it is reasonable to assume that they gave particular attention to them and that their reported figures represent in each case the mean of several estimations. The inevitable conclusion is that the results on routine specimens would have been far worse, due to the greater inaccuracy of tests on blood, and to sampling errors.

This view is supported by the work of Wooton and King (1953) in this country. They sent aqueous solutions to 36 and blood samples to 21 different Service and civilian hospitals. Their findings, calculated as a percentage of the mean, are shown in Fig. 5 and clearly demonstrate the greater scatter obtained when dealing with blood specimens.

On these surveys the estimations were all conducted on subsamples of a single original specimen and the sampling error was therefore eliminated. This is an error which rears its ugly head throughout hospital pathology. It is well recognized that samples may not be truly representative of the whole circulating blood, and that values may differ according to whether the specimen is venous or capillary; whether the blood was freely flowing; and whether stagnation was present in the part from which the specimen was taken. Even when these points are satisfactorily controlled there is still a considerable sampling error

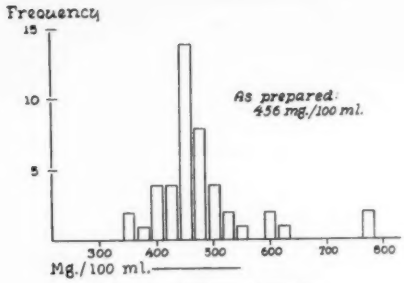

FIG. 1.—Sodium chloride.

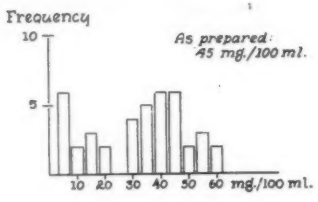

FIG. 2.—Urea.

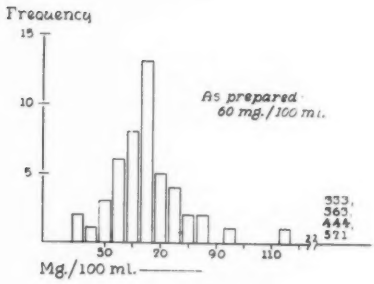

FIG. 3.—Glucose.

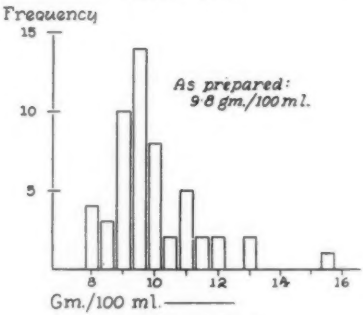

FIG. 4.—Hæmoglobin.

Figs. 1, 2, 3 and 4 have been reproduced by permission of Belk and Sunderman and the publishers of the *American Journal of Clinical Pathology*.

due to variations in the blood itself from minute to minute. Biggs and Allington (1951) showed that in the case of hæmoglobin an average standard deviation of 1·6% on subsamples of a single venous specimen increased to 4·5% when separate venous samples were taken in rapid succession. The difference between the two standard deviations represents a sampling error due to a physiological variation unaffected by technique. The average standard deviation in Belk and Sunderman's figures for a single venous sample was 9·4%, so that the difference between the average standard deviations of 1·6% and 9·4% gives us some indication of the relative accuracy which can be expected between a first-class research department and a group of routine laboratories.

Biggs and Allington compiled a table (Table I), based on their standard deviation of 4·5%,

TABLE I.—ERROR IN ESTIMATING PERCENTAGE OF HÆMOGLOBIN USING THE M.R.C. NEUTRAL GREY WEDGE PHOTOMETER

Hæmoglobin level (%)	Calculated range of 19/20 observations on one individual	Significant difference (% Hb)
120	113–127	10
110	102–118	11
100	91–109	12
90	81–99	13
80	71–89	13
70	61–79	13
60	51–69	12
50	42–58	11
40	33–47	10
30	24–36	8
20	16–24	6

In the second column is indicated the range within which separate observations on one individual should fall. In the third column is shown the difference between two isolated hæmoglobin readings on one person which would suggest that a real change had occurred (calculated from the formula $2\sqrt{2S^2}$).

Reproduced by permission of Biggs and Allington and the publishers of the *Journal of Clinical Pathology*.

showing the expected range of error using the M.R.C. neutral grey wedge photometer. A similar table from Belk and Sunderman's figures would have to be based on a standard deviation of 14%.

The sampling error is of even greater significance in bacteriology. For example, the number of stools found positive in amœbiasis, bacillary dysentery and salmonella infections is very dependent not only on the method of collection of the specimen but also on the discrimination with which a part of it is selected for examination. In addition, an inherent error arises from the fact that the organisms appear in showers rather than as a continuously excreted stream. Similar considerations apply to the examination of sputa for tubercle bacilli and to many other bacteriological procedures.

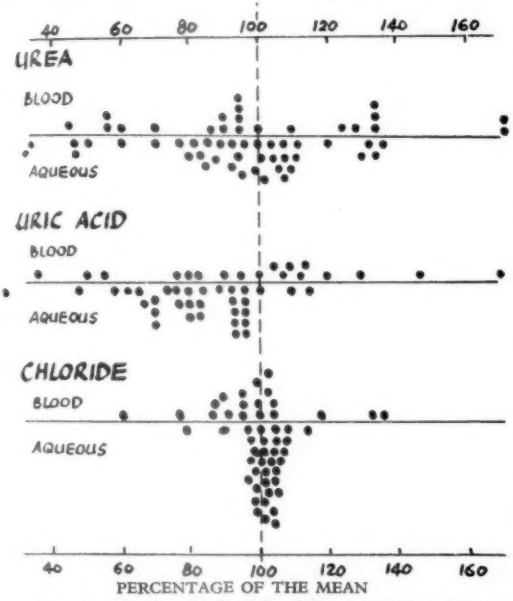

FIG. 5.—Results obtained by different laboratories on blood and aqueous specimens, each result represented by a dot.

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I think I have said enough to establish that the methods used in hospital pathology have an inherent inaccuracy which is greatly exaggerated by any laxity in technique. To ensure good technique there must be adequate initial training and this must be followed by continual maintenance of the interest of the technicians.

We are at a particular disadvantage at present because a very large proportion of Service technicians are National Servicemen who have only just completed their initial training. We have found that they vary very greatly in their proficiency; although all have passed the first civilian technical examination, the training of the majority has been unorganized and patchy, and only those from certain laboratories can be relied upon to be of a high standard. This is partly due to the fact that Service and civilian requirements differ, in that in civilian life a technician can be allowed to specialise in a very limited field, whereas in the Services he must be capable of working in any department of the hospital laboratory.

It is in the maintenance of a good standard by stimulating interest that co-operation between the laboratory and the clinical departments is so necessary; it is impossible to maintain interest without knowledge of the patients and in the face of a conviction that a large proportion of the tests are unnecessary. Yet some clinicians have the misguided idea that the laboratory should not be supplied with clinical details because they might influence unduly the performance of the tests. This shows a complete misconception of the pathologist's duties and functions. He must have full clinical details to ensure that the best use is made of each specimen; to maintain the interest of himself and his staff; to judge whether the results are reasonable or should be repeated; to help in their interpretation; and to make suggestions for further investigations. Clinicians should realize that a badly filled in form inevitably breeds bad results and is frankly discourteous. I have seen, accompanying a specimen of fæces, a form on which there was no history and only the request "chemistry and microscopy". Enquiry as to what was wanted brought the revealing reply "Well, I don't really know but the Consultant was here this morning and when he left he told me to get some investigations done". While I realize the need for gamesmanship on the part of Consultants when they wish to use the "delay ploy" in order to look at their books, ethics demand that other departments should not be involved.

The use of the laboratory as a diagnostic slot-machine, as well as being demoralizing to the clinician and causing unjustifiable inconvenience to the patient, produces an unnecessarily large proportion of monotonously normal tests; and monotony, particularly futile monotony, is the enemy of interest. This adverse effect was well illustrated in an extreme form by an

incident in the Middle East during the war. A senior technician was in charge of a serology laboratory devoted entirely to routine tests for syphilis. Investigations into the cause of a sharp rise in the number of positive results revealed that the technician, who by some oversight had served double the normal tour overseas, had introduced his own modification of the Wassermann reaction. He fished the blood clots out of their tubes, threw them against the wall, and if they stuck they were reported as positive, and if they fell down as negative.

An excess of normal results is also very liable to produce a false sense of accuracy. I once sat on a committee which was considering the relative merits of three serological tests. The figures presented were the results of some 76,000 tests performed in triplicate, and it was claimed that there was a 97% correlation. Enquiry showed that about 70,000 were negative by all three methods, and if the figures of the 6,000 with at least one of the three tests positive were considered alone the picture became very different—only about 60% correlation.

We have seen that in hospital pathology there is an inherent physiological sampling error, a basic technical error, and an error whose magnitude depends on the standard of technique, which in turn is greatly affected by the degree of liaison and co-operation between the laboratory and the clinical departments.

There is a further cause of error, unrelated to technique and in some ways more serious, since it leads not to mere inaccuracy but to actual mistakes, and this is the administrative one which is probably far more common than is generally realized. In transfusion work a mistake is likely to be attended by dramatically morbid results, and so be brought forcibly to the attention of all concerned. Discombe (1952) found 40% of transfusion reactions due to administrative errors, half of them committed by ward staff; Tovey (1953) found 37% due to the transfusion of blood intended for another patient through failure to check the label on the blood bottle.

I have personally known of two proved instances in the last three years where the theatre staff had put the wrong labels on a pair of biopsy specimens.

It seems reasonable to assume that similar mistakes occur in relation to other laboratory procedures, and that in some cases where the laboratory is abused for unexpected results which cannot be confirmed on repetition, they are due to administrative errors elsewhere. There is no doubt that as much care should be given to the checking of specimens for examination as is expended on the checking of drugs, since the consequences to the patient can be just as unfortunate, although legal proceedings are rare.

Before I set out to review the causes of inaccuracy of laboratory reports I mentioned the particular need we have in the Armed Forces for the greatest accuracy which can be achieved.

In the R.A.F. we are working towards this goal by paying special attention to initial training, by trying to encourage co-operation with the clinical departments, and by promoting research into technical improvements.

The problem of differentiation of early diabetes mellitus from other causes of glycosuria is particularly important as this disease is a complete ban on flying as aircrew. In recent years the significance of the two-hour value in a glucose tolerance test has been increasingly stressed, and in borderline cases it is regarded as the vital figure: 120 mg.% total reducing substances in venous blood by the Folin and Wu method is generally held to be the upper limit of normal.

We therefore decided to investigate the accuracy of glucose estimations in R.A.F. laboratories, and sent aqueous glucose solutions three times and serum twice to twelve different laboratories. The true values of the samples varied between 60 and 160 mg.% but for the purposes of illustration they have been scaled to a common figure of 120 mg.%. Each block in Fig. 6A covers a range of 10 mg.% and shows the percentage of the total tests falling within that range.

It is all too apparent that the chances of a mistaken diagnosis are very real, particularly when it is remembered that the estimations were carried out under the conditions of a trial, and sampling errors were eliminated.

It might be thought that any improvement on these figures would have to be by better technique rather than by any simple modification of such a long-accepted method. But the fact that a laboratory method has been accepted over a number of years is no safe criterion of either its accuracy or its perfection. Work carried out under the auspices of the Medical Research Council and published in the *Lancet* (King *et al.*, 1947) showed that the British Haldane standard, which had been accepted over the past fifty years as equivalent to 13·8 g.Hb% was in fact equivalent to 14·8 g.Hb% when measured by iron analysis. Correction of previous hæmoglobin surveys on this basis brought British normal figures into line with those of workers in other countries.

We decided to investigate the sources of inaccuracy in glucose estimation by the standard methods, and Squadron Leader S. Dische (1955) has produced a simple modification

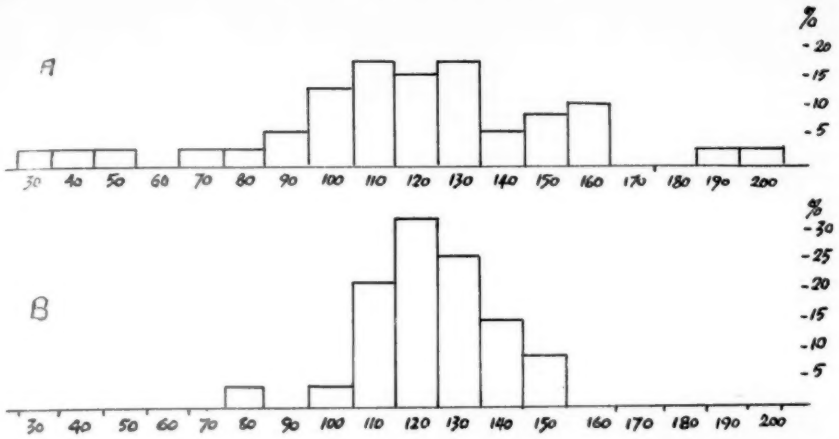

FIG. 6.—Glucose estimations performed by twelve R.A.F. laboratories using the traditional Folin and Wu method (A) and after changing to the modified method (B). All results scaled around 120 mg.% in 10 mg.% groups.

which we believe eliminates many of the causes of error. After the survey already mentioned had been completed we sent a further two sera and two aqueous solutions for glucose estimation by the new modified technique, without the correct answers for the previous specimens being communicated to the laboratories concerned. The results shown in Fig. 6B have been scaled around the 120 mg.% value as in the case of the previous survey.

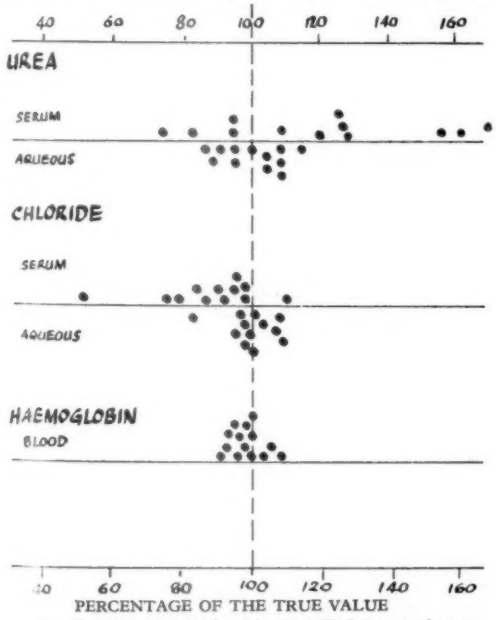

FIG. 7.—Results obtained by R.A.F. laboratories on serum, blood and aqueous specimens, each result represented by a dot.

The better grouping of the figures confirms that a large part of the previous scatter was due to inaccuracy of the classical method.

The few bad discrepancies all came from the same laboratory where there is no pathologist in charge. This illustrates the danger of the small laboratory with inadequate supervision, one of the many difficulties inherent in the administration of small hospitals.

We have carried out a further survey in which a blood sample was sent to 14 R.A.F. laboratories for estimation of hæmoglobin, and aqueous solutions were sent to 12 of these same laboratories for estimation of urea and chloride content.

The results (Fig. 7) have been calculated as a percentage of the true values, and it will be seen that the scatter of the urea and chloride figures is very similar to that found by Wooton and King.

The average standard deviation for the hæmoglobin estimations is 2·6% compared with 9·4% in the Pennsylvania survey and 1·6% in the experiments of Biggs and Allington. The improvement on the Pennsylvania figures is almost certainly because all hæmoglobin estimations in the R.A.F. are done by the same photo-electric method with a centrally standardized

neutral grey solution, and checks with test specimens are regularly carried out. The fact that the figures are not quite as good as those of Biggs and Allington is attributable to the inevitable increase in error when collecting figures from several laboratories as opposed to those all obtained under exactly the same conditions.

These surveys amply justify the principle of standardization of methods, particularly in the Services, where technicians are liable to become confused when on posting to a new laboratory they find a new set of techniques. We have now issued notes on recommended standard methods for hæmatology, and similar notes covering the rest of clinical pathology are in the course of preparation. No orders are issued to pathologists compelling them to use the recommended methods, because we consider every doctor must be allowed professional freedom, but trade tests for technicians are based on them, and the advantages of using them are pointed out. We shall send out test solutions and specimens at regular intervals, to detect defects in apparatus, standards or reagents, and at the same time we shall continue investigations to improve existing methods.

New methods should always undergo a period of controlled trial before routine adoption, and it is important that every laboratory procedure should be assessed in relation to the environment in which it is to be used. A method which is extremely accurate when employed in a research laboratory by highly specialized technicians may in routine practice give less consistent results than some simpler and theoretically less accurate procedure. Similarly a technique or reagent which is highly satisfactory in this country may be quite unreliable under the conditions prevailing in the tropics. We have also to bear in mind that, as far as possible, standard methods for Service laboratories should be applicable under field conditions in wartime.

It is my belief that the hospital laboratory, particularly in the Services, will become more and more the focal point of medicine, where all the "ologies" converge, in diagnosis, therapeutics, and research; but only by co-operation between the clinical departments, the hygienists, the administrators and the laboratory can full value be derived from the facilities available.

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Surgeon Vice-Admiral Sir Alexander Ingleby-Mackenzie considered that it was most important that the training of Service laboratory technicians should keep step with the increasing development of pathology and the improved methods continually coming into use. Accordingly, it would be necessary for all Services to watch this factor, and in view of it possibly to amend the length of training of their technicians and their curriculum from time to time. He further supported Group Captain Stamm in the need for accurate and adequate completion of the forms sent with specimens for laboratory investigation. He remarked that this was necessary in all walks of medical life, and recalled how, when he himself was medical specialist at R.N. Hospital, Plymouth, he once had a case sent in to him for admission with a form just stating "N.Y.D. yellow"!

Major-General W. R. D. Hamilton: I can heartily endorse the remarks of Group Captain Stamm in his appeal for closer co-operation between the physician and the pathologist. I should like to say that not only must the physician visit the laboratory to discuss his cases, but the pathologist ought to be encouraged to come to the wards to see the patients from whom he has obtained various specimens for examination.

When I was a Physician-in-Charge of medical wards, I found I got the best service from those pathologists who adopted this practice. Incidentally, human interest is added to the routine bench work of the laboratory by this means.

Section of Physical Medicine

President—DORIS BAKER, M.D., F.R.C.P.

[*April* 13, 1955]

DISCUSSION ON THE TREATMENT OF BACKACHE BY TRACTION

Dr. E. J. Crisp: Any new method of treatment requires prolonged clinical trial before its worth can be accurately assessed. The conclusions to be drawn from a short series of cases can be very misleading and far too optimistic. For example, a review of the first 50 cases I treated by traction showed that all 17 cases of acute lumbago obtained relief. I have never obtained comparable results since. Nevertheless it is extraordinary how often one may have a run of precisely similar cases.

I have used traction for a number of years now and should have had sufficient experience in its use to know what it can and cannot do. Even if spinal traction has not entirely fulfilled my original high hopes, it has proved a most valuable weapon in the treatment of many painful conditions of neck and back. Provided the right case is selected and the correct technique employed, it usually gives relief.

When I started using traction I was still an ardent disciple of the prolapsed disc. Believing that, if such pathological conditions as tubercle or new growth had been excluded, the usual cause of pain in the back was a disc protrusion, I imagined that by means of spinal traction it should be possible to reduce the prolapse and that after one or more treatments it would stay reduced. A moment's thought should evince that this was wishful thinking for the nucleus is contained within the annulus under considerable pressure. Therefore, though traction may temporarily reduce the prolapse it will obviously tend to recur directly traction is released.

When pain in the back arises from a displaced annular tag I think traction may well correct the condition, especially if the posterior longitudinal ligament is intact. I also feel that traction sometimes gives relief in the case of the contused disc with incipient protrusion, by which I mean the rupture of a few annular fibres only so that little or no bulge occurs. But the one type of disc lesion that spinal traction is unlikely to benefit is complete nuclear protrusion in the lumbar region: and still more so if it has progressed to "extrusion". But the fact remains that by means of traction or manipulation (or both) we can so frequently give relief, and often dramatic relief, of pain that clearly the symptoms cannot always be due to a disc lesion and there must be other causes of pain in the back.

It is an odd fact, but very true, that as each new theory comes along we forget everything we have previously learned. Twenty-five years ago we accepted Putti's theory (1927) that lumbar pain and sciatic pain might be due to an inflammatory condition involving one or more zygapophyseal joints. Furthermore, when we treated such cases in the manner he recommended, recovery was the rule. Shortly before the war we acclaimed Sir Thomas Lewis's and Professor Kellgren's exposition on referred pain and readily agreed that a sensitive intervertebral ligament might well give rise to sciatic pain (Kellgren, 1939; Lewis and Kellgren, 1939). By seeking out the painful ligament, injecting novocain and mobilizing the spine we frequently cured the patient. Surely we should pay more attention to the observations of these great men.

We are apt to make the mistake of focusing attention on the "prolapsed" or "slipped" disc to the exclusion of other equally important intervertebral structures. Now, unlike most other bodily structures the disc tends to degenerate comparatively early in life, especially in those regions of the spine where strain is greatest. Most people over the age of 50, if X-rayed, will be found to have one or more narrowed discs in the lower cervical region. This is because the nucleus has lost its power of osmosis, is dehydrated and consequently narrowed. Though there may be changes in the neurocentral joints, usually there is no pain in the neck or arms. The radiologist may report that there is evidence of a disc lesion but this does not mean that the disc has prolapsed: it has in fact merely degenerated. X-rays should be correlated with the physical signs, for paradoxically it often happens that when a severe lumbar disc protrusion gives rise to acute pain in the back and leg, the only abnormal X-ray findings will be scoliosis or a reversed lumbar curve, and the report will state "No evidence of a disc lesion".

Degeneration of a disc is a slow process and it may take a number of years before it gives rise to pain, and, when it does, the pain frequently arises in the posterior joints rather than the disc. In a paper read to the Congress of the English Speaking Orthopædic Associations

Macnab of Toronto described the changes he had found in the posterior joints following disc degeneration (Harris and Macnab, 1954). In consequence of the disc narrowing, the superior facet overrides the inferior facet, and this is followed by erosion of articular cartilage, osteoarthritis and thickening of synovia and capsule. In several specimens Macnab found an actual loose body in the zygapophyseal joint. By correlating these various facts and thinking in terms of intervertebral derangements rather than disc lesions, I have begun to understand why traction or manipulation so frequently relieves, but on occasion fails and even aggravates the condition. It has become evident to me that the incidence of genuine disc protrusions or extrusions is far less than is generally supposed, and that in their treatment manipulation or traction has, very often, little to offer. For this type of case bed rest or a plaster jacket is usually the treatment of choice with laminectomy as the last resort should these conservative measures fail.

The Intervertebral Joint

Let us consider in a little more detail the individual structures comprising the intervertebral joint, both in regard to the way in which they may give rise to acute and chronic pain, and the tendency towards spontaneous recovery or otherwise. Firstly the disc:

Acute episodes.—The annulus may rupture partially or completely following moderate or severe trauma, giving rise to acute lumbago and possibly sciatic pain. This is a condition which tends to recover spontaneously with adequate rest, the tear in the annulus being repaired by scar tissue.

Chronic episodes.—The disc may become narrowed by a process of slow degeneration which may or may not be the sequel of trauma. In due course this may result in chronic backache and sometimes pain which radiates to a limb. It is a chronic condition and spontaneous recovery is seldom the rule.

The Zygapophyseal Joints

Acute episodes.—In certain regions of the spine, especially the cervical and lumbar regions where flexion and rotation are free, it is sometimes possible at the extreme of movement for the synovial membrane to prolapse between the facets and become impacted when the spine is extended. This gives rise to acute pain and the normal curve, whether cervical or lumbar, becomes reversed: and again a zygapophyseal joint will react like any other joint if subject to strain or sprain—pain, stiffness or even synovial effusion resulting. Other obvious causes of acute pain arising in the posterior joints are subluxation or locking due to a loose body.

Chronic episodes.—Degeneration and narrowing of a disc affects the normal relationship of the facets and leads to erosion of articular cartilage, osteoarthritis and capsulitis, this last condition being the source of chronic pain. Any form of trauma may well aggravate still further an already sensitive capsule, leading to increased pain.

The Neurocentral Joints

In the cervical region disc degeneration affects the neurocentral joints of Luschka and their capsules rather than the zygapophyseal joints. Though the condition will often be symptomless trauma may well invoke an inflammatory response in an already thickened capsule, giving rise to pain in the neck which may radiate down the arm.

The Intervertebral Ligaments

We should not think in terms of disc and posterior joints alone. There remain the intervertebral ligaments, structures richly endowed with sensory nerves, which will give rise to pain in any form of intervertebral derangement, whether acute or chronic. Furthermore the ligamentum flavum responds to trauma by degenerative changes, the elastic fibres being replaced by fibrous tissue. The ligament becomes considerably thickened and movement is restricted in consequence.

Treatment

Traction frequently relieves pain, by releasing the nipped synovial membrane or subluxation, stretching the tight and painful capsule or ligament, or even freeing an adherent nerve root, but I find it difficult to imagine traction permanently reducing a nuclear protrusion unless the annular lesion is a small one. However, provided the technique is correct, even though traction should temporarily increase pain in the case of a genuine disc protrusion, it seldom aggravates the lesion.

Technique

Whether we are applying traction to the lumbar spine or the cervical spine, correct posturing of the patient is all-important. In the lumbar region traction is given with the

patient lying prone and it is essential that the lumbar spine is in the flattened or neutral position. This is done by placing a pillow of suitable size under the abdomen. We wish to stretch the capsules of the posterior joints and the intervertebral ligaments. If the lumbar spine is too lordosed we shall apply our stretch to the abdominal wall or the mesentery and may cause the patient severe abdominal discomfort.

I use a very simple table, the top of which has one fixed and one movable portion. The patient's shoulders and thorax are firmly secured to the fixed portion, while the lumbar region, pelvis and legs lie on the movable portion. Traction is applied through a pelvic belt attached to two spring balances at the foot of the table by two adjustable ropes, one on either side. I use a moderate poundage, 40–80 lb. according to the type of case. This may sound so little as to be useless, but by virtue of the movable top, friction between body and table is eliminated and all the pull applied to the patient. An advantage of the twin ropes is that they may be adjusted so as to apply a stronger pull on one or other side of the trunk if thought necessary.

Cervical traction should be given with the patient lying supine. Once again correct posturing of the neck is paramount. Thus the neck should be well flexed to apply traction to the posterior joints, and moderately flexed to stretch the neurocentral capsules. When we want to increase extension, as is the case when posterior marginal lipping causes pressure on the cord, traction is given with the neck in the neutral position. Traction may be carried out manually or by means of Sayre's sling, using weights and pulley. In this case I use 25–45 lb. for ten to twenty minutes.

As regards what should be manipulated or stretched, and when it is advisable to leave well alone, one could write a whole book on the subject if only time permitted and one had the energy. But, briefly, to deal first with the lumbar spine.

The Lumbar Spine

Acute conditions.—Lumbago, if rested, is a condition which often tends to recover spontaneously in the course of a few days; therefore if the pain is already subsiding when the patient is first seen, I tend more and more to leave well alone, especially in the older age groups. Though many cases respond strikingly to traction or manipulation many others are aggravated.

Acute lumbago with a reversed lumbar curve and of sudden onset is, I think, often due to a nipped synovial fringe. When this is so, as is only to be expected, the condition responds like magic to traction. It is the case with the lumbar spine held in tight lordosis by muscle spasm which presents the problem. Though sometimes relieved dramatically by traction, in my experience such treatment more often aggravates the pain and I think it is because a ruptured annulus is responsible for the symptoms. Nevertheless, I frequently give the patient a gentle trial traction, and if it reduces the pain repeat the treatment. But should it aggravate the pain I advise rest or even a plaster jacket. I occasionally use an epidural injection, but am not altogether convinced of the efficacy of this method.

When the patient has acute sciatica, whether or not in association with lumbar pain, I seldom hesitate to try traction, for it frequently gives relief. But when this happens I feel that if a disc lesion was responsible for the condition it was probably a small one, and that it was more likely the symptoms arose in the posterior joints. There is, however, a time and place for everything. Following a period of bed rest or plaster jacket the crural pain, though diminished, sometimes remains a source of considerable discomfort. Traction or manipulation at this stage is often successful, presumably either by completing the reduction of the prolapse or freeing an adhesion.

There remain a number of cases which by their history, symptoms and physical signs advertise themselves as severe disc lesions with root pressure, and unlikely to benefit from traction. Though such cases may derive temporary relief while pulled out on the traction table the trouble starts when we reduce the traction, and the pain returns with increased intensity. I have on occasion spent more than an hour trying to get the patient down.

Chronic conditions.—It is in the treatment of the older age groups with chronic low back pain that I have found lumbar traction of the greatest value. It may sound a dangerous procedure to manipulate or apply traction to a lumbar spine with marked degenerative changes, but in my experience this is not the case. When discs become narrow they lead to secondary changes in the posterior joints, where thickened and sensitive capsules give rise to chronic backache. By stretching the thickened capsules I have found it possible to relieve many patients with chronic backache. Naturally one must select the right case, but fortunately selection is facilitated by easily recognizable distinguishing characteristics. Few patients have backache for twenty-four hours of the day. It will be found that whereas one type of patient will complain that bed rest relieves the pain while activity aggravates it, another class of patient will tell you precisely the reverse. It is the patient whose lumbar pain is relieved by activity who derives such remarkable relief from several treatments on

the traction table. A useful analogy would be the chronic sprained ankle which stiffens up when rested, loosens up if exercised, and is only completely cured by manipulation. In like manner crural pain, whether neuritic or referred, when it occurs in association with degenerative lumbar changes frequently responds to manipulation or traction.

The Cervical Spine

It is remarkable how often pain in the neck develops during the night. The patient retires to bed without a care in the world only to be woken up in the early hours of the morning by acute pain in the neck which is aggravated by every movement.

If by careful differential diagnosis we exclude pathological causes such as tubercle, new growth, &c., painful cervical conditions may be placed roughly in three categories.

(1) In the younger age groups the cause of the pain, more often than not, is a nipped synovia or subluxed posterior joint. X-rays, apart from showing a cervical kyphosis, are negative. The response to manipulation or traction is dramatic.

(2) In the older age group the pain, though first felt in the neck only, sooner or later radiates to the shoulder or arm. X-rays usually show one or more degenerated discs whose presence was previously unsuspected. The symptoms may be the result of a displaced tag of annulus or more often the result of trauma which causes an inflammatory reaction in the capsule of the neurocentral joint. Once again the response to manipulation or traction will be most gratifying, though the period of treatment may often be protracted. Many cases of this type that have derived no relief from prolonged bed rest are rapidly improved by cervical traction.

(3) There remains a small group of patients whose symptoms are due to disc lesions, major or minor, often the result of severe trauma. When there are marked root symptoms following protrusion the ideal procedure is to hospitalize the patient and apply sustained traction for as long as may be necessary. The less severe case will often respond to daily treatments.

In the cervical region there is a more reasonable prospect of a small protrusion staying reduced than there is in the lumbar region. My personal feeling is that acute cervical disc episodes are more often due to trauma deranging an already degenerated disc, than to the sudden rupture of a healthy annulus.

The Dorsal Spine

Though one can often relieve pain in the lower dorsal region by traction I prefer manipulation for the middle and upper dorsal regions. It is only by this means possible to deal with pain which arises in the costo-vertebral articulations. The thoracic cage affords considerable protection to the dorsal discs, so that whereas degeneration of the discs is a common occurrence, acute protrusion is probably very infrequent. Many obscure pains which may radiate to the front of the chest or abdomen undoubtedly have their origin in a dorsal derangement and may be relieved by manipulation or traction.

Conclusion

Used correctly spinal traction can do little harm, but each case must be treated on its merits. There is a place for physiotherapy, rest, plaster, manipulation and traction, and frequently a combination of several of these measures is the ideal.

There may appear to be certain inconsistencies in my remarks! After making the statement that it would appear impossible for traction to reduce and keep reduced a large lumbar protrusion, I proceed to advocate a trial of traction on every case of sciatica. My excuse must be that "it is the exception which proves the rule", for occasionally one gives the patient rapid relief by means of traction when such a measure appeared a forlorn hope.

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Dr. J. H. Cyriax (*in absentia*, read by Dr. R. Barbor): Sustained traction suggested itself to me in 1949 when, pondering the reason for the success of rest in bed in lumbago, it dawned on me that the benefit arose from the avoidance of a compression strain on the joint. The next step thus became obvious, active decompression: in other words, traction. I had already tried manual traction during the reduction of cervical and thoracic disc displacements and found it invaluable, but to my surprise it had proved useless in aiding

manipulative reduction at a lumbar joint. The reason for this was soon apparent, when I discovered by radiography that traction for a few seconds doubles the width of the joint-space at the cervical spine (Fig. 1) but increases it by only a tenth at the lumbar joints (Fig. 2). Fig. 3 shows the traction couch in use, a simplified version of the model illustrated in the *British Medical Journal* (Cyriax, 1950). The traction must be constant, so that the muscles tire and the strain falls on the joint. I mention this because osteopaths use a machine with an electric motor under it giving intermittent traction each few seconds. This I consider much less effective, but it impresses patients enormously.

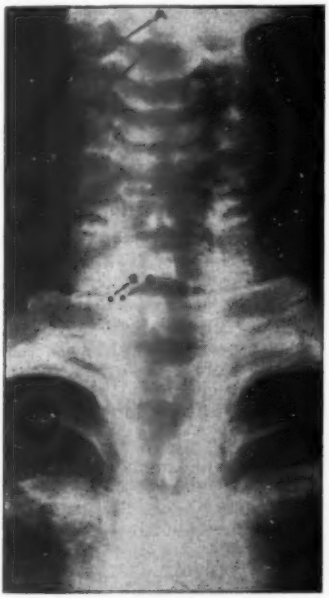

FIG. 1.—Manual traction on cervical spine. Two radiographs have been superimposed, corresponding at the first thoracic vertebra. The first was taken before, the second during, a few seconds' manual traction. Note that the joint spaces have almost doubled in width.

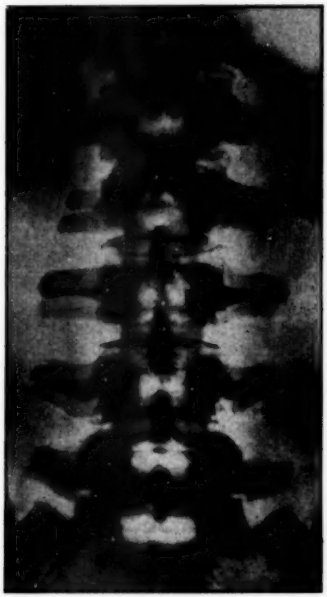

FIG. 2.—Mechanical traction on lumbar spine. Two radiographs have been superimposed corresponding at the sacrum. The first was taken before, the second after, fifteen minutes' mechanical traction of 120 lb. Note that the joint spaces have increased in width by only one-tenth.

FIG. 3.—Traction couch.

EFFECTS OF TRACTION

(1) Distraction of the vertebral bodies, thus enlarging the space into which the protrusion has to recede.

(2) Tautening the posterior longitudinal ligament. When the slack on the ligament is taken up, it can no longer bulge posteriorly and thus exerts centripetal force on the adjacent annulus.

(3) Suction, tending to pull back protruded material into the joint.

Technique

The patient lies on the couch; some do better supine, others prone. He is treated once or twice a day for half to one hour each time. A small woman may need 100 lb., a large man up to 200 lb. A thoracic and a pelvic belt are applied, and the straps attached to the ends of the couch. The physiotherapist turns the wheel and gradually increases the traction until the patient feels he has enough tension. After a short while he may ask for more. The force is measured on a spring balance which serves two purposes: first to measure this force and thus enable uniform treatments to be given; secondly, to take up slack if either belt slips slightly. As soon as the traction becomes effective, certain alterations in the pain are felt by the patient.

(1) The pain usually ceases. If not:

(2) A unilateral lumbar pain may become central.

(3) A root pain may become a lumbar pain.

(4) A root pain may shorten, for example it may move from the calf to the thigh or buttock.

(5) A root pain may remain in the same place but become less intense.

(6) The pain may remain unaltered.

The patient must attend daily; if he cannot do that, he is not accepted for treatment at all. Treatment is abandoned if he has not begun to improve after twelve sessions. If he improves he continues until reduction is complete, normally one to four weeks. The only exception is the uncommon patient with constant backache of some years' standing causing marked limitation of straight-leg raising on both sides. Apart from operation, these patients are unrelievable except by traction, which may have to continue for two or three months.

Indications

Unlike the state of affairs at the cervical joints, where the indications for manipulation and traction are wholly separate, these two methods of securing reduction are partly interchangeable at the lumbar spine. Lesions reducible by manipulation and not by traction at this level and vice versa are of course encountered, but there is a number of intermediate cases for which either method is satisfactory. Since manipulation is effective at once and traction takes some days at least to become so, in all cases of doubt I manipulate there and then, and put on to traction only those in whom manipulation fails or is only partly successful.

The indications for traction are:

(1) *Nuclear protrusion.*—In typical cases, the onset is gradual, the pain often coming on some time after exertion or after the patient has sat some while. The same suggestion arises if any of the lumbar movements other than flexion cause pain in the limb rather than in the back, or if pain is set up when the protrusion is pinched, that is, when side-flexion towards the painful side hurts.

(2) *Failure of manipulation.*—Sometimes a displacement appears reducible by manipulation, judged by the history and signs, but the attempt fails. Primary postero-lateral protrusions, in which the first pain is felt in the thigh or calf without any backache, are never reducible by manipulation; only traction avails.

(3) *Impaired root conduction.*—Traction should be used when there are two or more neurological signs, e.g. a weak muscle and an absent ankle-jerk or cutaneous analgesia; manipulation is sure to fail. However, the induction of epidural anæsthesia is often the treatment of choice when neurological signs are severe. It should be remembered that neurological signs may be the result of damage from a previous attack of sciatica, and their relevance to a subsequent attack must not be assumed too lightly.

(4) *Relief from pain.*—Cases of sciatica of some months' standing are encountered, in which the treatment of choice is to leave the protrusion where it is and merely ease the pain by the induction of epidural local anæsthesia. Occasionally the injection brings no lasting relief. If the pain is considerable, traction has to be employed.

(5) *Fourth sacral reference.*—Whatever method is adopted, cases with pain referred to the coccyx or genital area must be regarded as in danger of the development of a fourth sacral palsy and should be treated with great care. I, for one, never manipulate in such cases. Traction and epidural local anæsthesia are safer and therefore can be employed.

(6) *First and second lumbar disc lesions.*—Disc lesions at these two levels are rare, and I have never yet succeeded in reducing one by manipulation. By contrast, traction has been successful.

(7) *Recurrence after laminectomy.*—In these cases manipulation is seldom successful, but can safely be attempted. Traction is more often effective but in all patients who have had a laminectomy the prognosis is more unfavourable than in those who have never had the operation.

Contraindications

The contraindications to traction are:

(1) *Purely annular displacements.*—These should be reduced by manipulation immediately the diagnosis is made. An accurate assessment of the nature of the protruded material is therefore essential. The history is usually of sudden onset, with or without a click, often when the lumbar spine is extending after flexion. Certain signs show that an annular displacement is present. The more common are:

(*a*) A painful arc during trunk flexion.

(*b*) Pain caused by side-flexion away from the painful side.

This applies particularly to elderly patients (over 60) whose protrusions nearly always respond better to manipulation than to traction.

(2) *Lumbago with severe twinges.*—This is unsuited to traction. The pain ceases as soon as the traction is applied but when it is released even more agonizing twinges appear and the patient may be unable to get off the couch for an hour or two; when at last he can, he finds himself no better for the ordeal. Should such twinges come on, an epidural injection usually stops them lastingly.

(3) *Impaired cardiac or respiratory function.*—Patients so afflicted may find the thoracic band too much of an embarrassment.

Maintenance of Reduction

After reduction by traction of a protrusion causing lumbago or sciatica, redisplacement is just as much a possibility as when the reduction has taken place spontaneously, during recumbency, or by manipulation. Hence no lasting result can be expected unless the patient is given clear postural instruction on the maintenance of reduction. The correct methods of sitting, stooping, bending and lifting must be explained. These are simple and the patient must develop the habit, for they are no less important than the reduction itself. This can also be maintained by a corset, properly fitted with shaped metal lumbar supports to fit the lumbar lordosis, but I regard as an error the common practice of applying a corset or a plaster without reduction of the displacement first.

Results

The only published figures are by Bang and Sury (1955) who reported good results in 50% of patients selected purely on a basis of intractability by all other methods, including in some cases laminectomy; hence they represent the results of traction at their worst. They first used one of my couches, and then invented an improved model of their own.

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Dr. B. G. B. Christie:

It was decided, at the Middlesex Hospital, to undertake an investigation to evaluate the place of traction in lumbar backache. This paper deals entirely with the pilot series which is to be a preliminary to a larger scale investigation.

It was decided to treat half the patients in this series with traction, and the other half with a bland pill. This latter would approximate closely to their receiving no treatment at all, and consequently allow one to compare the results obtained by traction with those that might be expected to obtain as a result of the natural history of the condition. It is appreciated that by giving the patient even a bland pill some effect of a psychological nature may be expected, but if this be true, it must also be true of the traction table with its impressive equipment.

The investigation started early in 1954 when it was decided to hold a special clinic each

week to assess patients before and after treatment. The patients referred to this clinic were carefully selected as all patients with psychiatric or hypochondriacal histories were excluded, as also were those with congenital anomalies of the lumbar spine or sacro-iliac joints. It was not, however, intended to exclude spondylolisthesis or spondylolysis, but unfortunately none has been referred and so none appears in the series. All patients were carefully investigated to exclude other pathologies such as tuberculous caries or secondary deposits.

The patients that were eventually included were treated either by traction or the bland pill, every attempt being made to place roughly similar cases equally in either group. The total number of patients treated was between 60 and 65, there being just over 30 in each group.

All the patients complained of backache in the lumbar region with or without reference of pain down the legs. According to the examination findings they were classed as having root signs, or no root signs. Under the heading of root signs have been included limitation of straight-leg raising on the affected side, as compared with the unaffected leg, alteration in the tendon reflexes, or evidence of motor or sensory involvement. If none of these criteria was elicited the patient was classed as having no root signs.

Some difficulty was experienced in dividing up the patients into acute and chronic. It was decided, for the purpose of this series, to class as acute all backaches of recent origin, and the arbitrary period decided on was six weeks. Therefore those cases in the series classed as acute all have histories of six weeks or less. Backaches of longer duration than this were classed as chronic. It will be appreciated that in many cases it was possible to make a more accurate anatomical or pathological diagnosis, but owing to the confused nature of the nomenclature in lesions of the back, this controversy has been avoided in this series.

All patients were subjected to a searching history and clinical examination, X-rays were taken, and the sedimentation rate estimated. Subjectively the patient's pain was recorded according to a pre-arranged classification. This was as follows:

Grade 0	No pain.	
Grade I	Pain of nuisance value only.	
Grade IIA	Pain of more than nuisance value but not crippling.	No time off work.
Grade IIB	Pain of more than nuisance value but not crippling.	Time off work.
Grade III	Crippling pain. Incapable of work.	

In practice this classification worked satisfactorily, and no difficulty was experienced in allotting patients to their respective grade before and after treatment.

The traction table used was of a standard type similar to that used in many hospitals, and was in fact a combination of what were thought to be the better features of several tables being used in London. Traction was exerted by a geared wheel on the side of the table so that the lower part moved away from the fixed upper end. The degree of traction could be measured by the spring balances between the pelvis and the lower end of the table, each balance measuring up to 112 lb. Therefore, with the two in parallel, it was possible in theory to measure degrees of traction up to 224 lb. In practice this was not in fact possible as the limiting factor was the fixation of the upper end of the patient, and at forces in the region of 150 lb. the patient tended to slip.

Those patients who were treated by traction were all treated in the prone position. Traction was exerted until the patient was either relieved of pain or his pain aggravated. In those whose pain was relieved the degree of traction employed was noted and it was maintained at this level for twenty minutes. After this time had elapsed the traction was slowly eased off over a minute or two. This consituted one treatment and patients were treated three times a week for four weeks. All these treatments were carried out and supervised by experienced physiotherapists. In those patients who were aggravated by traction the force required to increase the pain was noted, and if they were made worse on two or three consecutive occasions treatment was abandoned and deemed to have failed. It was our experience that in those patients aggravated by traction, the force employed was frequently small, being in the region of 50 lb. or less, also that the degree of pain in these patients was invariably more severe following such an episode.

Those patients in the series that were not treated by traction were informed that their backache could best be treated at the moment by pills, and were prescribed the bland pill under the name of Tabs. Dormosan B. These tablets were not given any special "build up" in the eyes of the patient, and they were instructed to take two tablets three times a day, and if the pain was very severe, this could be increased by a further two tablets. These patients were sent away for four weeks and reassessed at the end of that period. The tablets in fact contained lactose.

The results of this pilot survey must be considered in the light of the fact that all observations were made by one person, therefore observer bias cannot be excluded. The small number of patients may also give rise to misleading results. When the survey was started over a year

ago it was hoped that at the end of one year we should have been able to collect about 150 to 200 patients, having half in each series. It will be appreciated that the patient complaining of backache is first seen by his family doctor who either immediately, or following some conservative home treatment, refers him to the outpatient department of the hospital, where in due course he is seen by appointment and examined. Radiological and laboratory investigations are ordered, and if he falls into the suitable category he is referred to the special clinic which was performing this survey. These various stages necessarily entail a certain time lapse, and of the cases referred, I was continually disappointed in the early stages by patients informing me that their backache was now better, or that instead of a backache, which according to the history had been present for weeks or years, they now have a pain in their shoulder, neck, knee or elsewhere. These patients were, of course, discarded from the series and treated appropriately for their new complaint. Unfortunately, no record has been kept of the number of patients so discarded, but I know that they exceed 50% of those seen, and believe that the figure may be as high as two out of three. This accounts for the large wastage, and has to be borne in mind in the interpretation of the results of those that were included in the series.

By classification into acute or chronic backache according to the criteria previously mentioned one gets the two main groups, and these are then each further subdivided according to whether there were objective root signs present or not. It will be seen from Table I

TABLE I.—DISTRIBUTION OF CASES IN THE TWO SERIES

Series	Chronic with signs	Chronic with no signs	Acute with signs	Acute with no signs
Traction ..	30%	51%	13%	6%
Dormosan ..	30%	50%	15%	5%

that the numbers in each of these four groups were roughly the same in each series. All numbers have been shown as percentages and fractions have been approximated to the nearest whole number.

The gross results of treatment are shown in Table II where patients are divided into three

TABLE II.—COMPARISON OF RESULTS OF TREATMENT IN THE TWO SERIES

	Better	Worse	Same
Traction	30%	18%	52%
Dormosan	30%	5%	65%

groups following treatment, better, worse, or the same. The placing of patients into one of these three categories was done when they were assessed at the end of four weeks' treatment, and by using such a broad classification little difficulty was encountered in assessment. Some of the patients who were classed as better or worse had appropriate alterations in the physical signs, but in the majority the improvement or otherwise was entirely subjective, such physical signs as limitation of straight-leg raising or forward flexion remaining unchanged.

From Table II it will also be seen that the majority of patients in each group were unaffected by the treatment, 52% in the case of those on traction and 65% of those on the bland pill. 18% of those treated by traction were aggravated, and 3 patients required admission to hospital, one later requiring a laminectomy. 5% of those having the bland pill were worse, but none so bad as to need admission. On the credit side are 30% in each group that improved. Several of the results with traction were quite dramatic, the patients not requiring to complete the course of twelve treatments, as they became entirely pain-free after several treatments only. This, however, was not entirely confined to those receiving traction, as several patients on the pill informed me that after taking it for some days all their pains had disappeared and had not recurred.

At this stage one should again face the question of whether traction is an effective form of treatment in lumbar backache. From the results of this series we relieved 30% of cases, and in the majority of these cases there was no backache after successful treatment. In the minority the improvement amounted to nothing more than an amelioration of the symptoms. As a disadvantage one has to consider the 18% that were worse during or after treatment. No doubt with a more exact knowledge of the nature of the cases that respond, and those that do not one could reduce the number of cases that were aggravated. This was the second aim of this investigation, namely to discover the most suitable cases for traction. Unfortunately, the small numbers to date do not allow any predictions to be made, but it is interesting to compare the results in chronic backache in the two series. Chronic backache formed 81% of the cases on traction and 80% of those on the bland pill, so formed the majority of the cases in both series.

Chronic backache with root signs showed results better than those of all cases considered together, where 30% were better, 18% worse, and 52% the same when treated by traction. The results as shown in Table III show improvement in 30%, deterioration in 10% and

TABLE III.—COMPARISON OF RESULTS IN CHRONIC BACKACHE

Dormosan				Traction		
Better	Worse	Same		Better	Worse	Same
17%	0	83%	With root signs	30%	10%	60%
30%	10%	60%	Without root signs	24%	29%	47%

60% who were unaffected. These figures are significantly better than those treated by the bland pill where only 17% were improved. In chronic backache without root signs the very high figure of 29% aggravated by treatment was found.

It is unfortunate that the number of acute backaches according to the criteria has been so small, as it has been said that traction is often of value in these cases. No figures are presented from this series for acute backs, but of the small number treated by traction none have been worse following treatment.

In considering traction as a method of treating lumbar backache the interesting question of what happens when one subjects the patient to the distracting force arises. In an attempt to answer this question two student volunteers were fixed to the traction table, and lateral view X-rays were taken of the lumbar spine before and five minutes after traction with a force of 75 lb. An experienced radiologist reported on the films and in his opinion there was a lengthening of the lumbar spine in both cases. The lumbar disc spaces were widened after traction, and in the case of the 5th lumbo-sacral disc, and that between the 4th and 5th lumbar vertebræ, the widening was 10–15% of the preliminary figure before traction. Precautions were taken to ensure that the distance between the patient and tube, and patient and film were identical in each case. It is interesting to note that this widening during traction got progressively less as one ascended the lumbar spine so that in both cases there was no measurable difference after 75 lb. traction for five minutes in the disc space between the 12th thoracic vertebra and the 1st lumbar. If this is true, and widening in the disc spaces in the lumbar spine is always genuine, whereas narrowing may be apparent only, then it would appear that traction is more likely to be effective in the treatment of lower lumbar than higher lumbar disc lesions. As, however, in practice the lower discs comprise the vast majority of disc lesions, this is probably of theoretical value only. If nevertheless widening does take place in the lower lumbar disc spaces with traction, then there must also be sliding of the facet joints which in the lumbar spine allow an appreciable range of flexion and extension.

It would have been interesting to subject these student volunteers to greater degrees of traction, but in both cases, and in several other normal people without backache who have been stretched, it has been the rule for increase of traction to cause a backache which increases with the tractive force. This differs from what is usually found when patients who have backache before treatment are subjected to traction. In most of the patients treated, with the exception of the 18% who were definitely made worse, the majority experienced considerable relief during the period of traction which in some cases was maintained for some hours following treatment. Unless this improvement was maintained from the end of treatment to being assessed, which was often a week, these patients were not regarded as having benefited from traction. This is a possible source of error if one sees the patients immediately after they have finished treatment, as then the majority are much improved, if not free of pain, only to be as bad the following day.

These observations are of interest in considering the pathology of disc lesions, especially if traction can exert a hydrostatic negative pressure in the nucleus pulposus, which is only presumptive. If, however, this is the case, then hydration of the disc tissue in the normal person, achieved by traction, falls fairly well into the category described by Charnley (1955) under the name of raised disc tension. It would also explain the relief of symptoms in patients with degenerate and desiccated disc tissue. Unfortunately, these statements are difficult to prove by scientific methods.

These are the results of a small controlled pilot series, and it is hoped that at a later date more conclusive results will be available.

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Section of Surgery

President—HAROLD C. EDWARDS, C.B.E., M.S., F.R.C.S.

[*April* 22, 1955]

MEETING AT KING'S COLLEGE HOSPITAL, LONDON

Thyroiditis

By SELWYN TAYLOR, M.Ch., F.R.C.S.

THYROIDITIS may be acute or chronic. The acute form is rare, due to blood-borne infection and seldom suppurates. Chronic thyroiditis is a convenient title which includes a number of conditions of unknown ætiology. The diagnosis is made by a combination of clinical, laboratory and pathological findings. A group of patients has been reviewed.

Hashimoto's (1912) thyroiditis (struma lymphomatosa, lymphadenoid goitre) occurs typically in women between 30 and 40, produces a moderately firm goitre with well-defined borders and progressive hypothyroidism. Split-needle biopsy confirms the diagnosis. Histologically, follicular cells show Askanazy changes, there is lymphocytic infiltration, lymphoid replacement and increased fibrous stroma. Treatment is thyroid by mouth, X-rays or relief of pressure by operation.

de Quervain's (1904) thyroiditis (granulomatous, giant-cell, pseudo-tuberculous, non-suppurative thyroiditis) is an acute febrile illness with moderate enlargement of the thyroid, pain radiating to the ears and raised sedimentation rate. Onset is often preceded by pharyngitis. Radioiodine uptake is reduced to zero. Spontaneous recovery occurs in three to twelve months. Diagnosis is confirmed by needle biopsy. Histologically there is infiltration by plasma cells and lymphocytes, follicles swell and disrupt, their nuclei aggregating to form pseudo-giant cells. Fibrous stroma increases markedly. Treatment by thiouracil, thyrotrophic hormone or cortisone gives immediate relief of symptoms but does not shorten the attack.

Riedel's (1896) thyroiditis (woody or ligneous struma) is a rare condition in which the thyroid and surrounding tissues are replaced by fibrous tissue. Diagnosis is usually made at operation for presumed thyroid cancer. Treatment is relief of tracheal obstruction.

[The various pathological changes were illustrated by lantern slides.]

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The Arterial Circulation in Ulcerated Legs

By L. T. COTTON, F.R.C.S.

IN chronic ulceration of the legs either the major arteries, arteriovenous anastomoses or arterioles may be affected.

"Arterial" ulcers are usually found outside the malleolar area where "venous" ulcers occur; they are often sited on the anterior aspect of the shin. They arise usually in patients of more than 60 years, are very painful, and do not respond to treatment. The peripheral pulses are absent and hypertension is usually present. X-rays of the legs reveal arterial calcification and arteriography shows extensive disease of the femoral and popliteal arteries. Arterial disease may also arise coincidentally in cases of venous ulceration.

Evidence has accumulated that arteriovenous anastomoses may be functioning in ulceration of the leg. Examination of casts of veins removed at stripping operations has confirmed that varices arise below the venous valves. This suggests that an increased blood flow may be at fault rather than an effect of an increased back pressure. Examination of ulcerated legs which have been amputated and injected has shown leakage of the arterial injection mass into the superficial veins. Arteriography in some cases has shown a rapid speed of venous filling.

Arteriolar disease is seen in the indurated plaques often found above the malleoli. These are very painful and slowly spread to involve a large area of the lower leg. The induration is identical to that commonly found around chronic ulcers. Histological examination of these plaques shows fat necrosis with fibrosis, obliterative endarteritis and foamy macrophages. An unexplained feature is the presence of cystic spaces in the dermis and subcutaneous tissues.

[This paper was illustrated by slides of the conditions described.]

The Anatomy of the Segmental Arteries of the Kidney [*Synopsis*]

By F. T. Graves, F.R.C.S.

The coincidence of two cases in 1952 in whom removal of a stone from a calix by nephrolithotomy resulted in persistent hæmaturia necessitating secondary nephrectomy, prompted the investigation of the distribution of the vessels within the substance of the human kidney.

The renal artery in post-mortem specimens of normal kidneys was injected with resin and study of the casts so formed showed that the distribution of the arteries within the substance of the kidney was constant, and upon this was founded the division of the renal parenchyma into five segments. These have been named the apical, upper, middle, lower and posterior segments. The upper and middle segments of the kidney lie in the anterior plane of the organ, the posterior segment lying in the posterior plane. The apical and lower segments, however, occupy areas in both the anterior and posterior planes. The main stem of the renal artery divides into an anterior and posterior division, the posterior division supplies the posterior segment, the anterior division supplies the remaining segments. The presence and distribution of these arteries is constant, the only variation being in their point of origin from the main stem artery, the artery to the lower segment being the most important from a practical viewpoint, its origin occurring at any point between the hilum and the aorta.

There is no collateral circulation between the segments. An artery supplying one segment was ligated before the injection of a specimen was made and as a result the area normally occupied by the segment was unfilled with resin. In case the molecular volume of the resin might be sufficiently large to prevent it passing along any small collateral channels which might exist between the segments, the specimens were also examined by renal arteriography using a radio-opaque material of small molecular volume. Arteriograms and also segmental arteriograms of the renal arteries were made which confirmed both the presence of the segmental arrangement and also the absence of a collateral circulation between the segments.

The work also showed that many of the so-called "aberrant" or "accessory" arteries are in fact normal segmental arteries whose origin from the main stem of the renal artery is more proximal than usual. Division of such vessels will result in avascular necrosis of the segments which they supply.

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For the full paper on this subject *see* Graves, F. T. (1954) *Brit. J. Surg.*, **42**, 132.

Symptoms Following Cholecystectomy

By Victor Parsons, B.M., B.Ch.

In this survey of 209 patients operated on by one surgical team in the years 1948–1954 it is shown that the operation performed for a worth-while reason is a success and that the incidence of symptoms referable to the biliary system is small following cholecystectomy. Of these patients 90% had gall stones, 30% had been or were jaundiced, 20% had the common bile duct opened, finding stone in at least half of these; only 4 had had pancreatitis.

Post-operative results.—3 died, all of whom had known cardiac lesions; among the others, followed on the average for at least five months on full diet, 22 were found with persistent symptoms: pain (in 20), flatulence and distension (in 15), vomiting (in 10), fat intolerance (in 9). The 22 separated out as follows:

(1) In 7 the symptoms had subsided.
(2) In 6 other lesions were found; recent peptic ulcers and hiatus hernia.
(3) In 6 persistent biliary symptoms.
(4) In 3 a strong psychogenic element.

The causes for return of symptoms can be grouped into three:

(1) Errors in diagnosis.

(2) A group whose symptoms and the presence of gall stones made operation advisable, but whose psychological constitution did not allow them to lose their symptoms.
(3) Persistent biliary dyskinesia.

This latter group were investigated thoroughly, in 3 intravenous cholangiography (using Biligrafin) showed a dilated duct, in 2 one of normal calibre and in 1 the duct failed to visualize. Liver function tests were normal. It can be suggested that they form a group where the gall bladder is not responsible for all the original symptoms. Thus the presence of cholecystitis and cholelithiasis are signs, on occasion, of a functional disorder of the biliary system as a whole, and in these patients the primary upset has not been focused on the gall bladder—thus removal may precipitate rather than relieve the symptoms. It has been maintained that the removal of a gall bladder without stone or inflammation makes return more likely, in this series 4 out of the 6 with definite symptoms had either cholesterosis or no evidence of inflammation.

In the discussion that followed, the incidence of pancreatitis following cholecystectomy in the elderly was mentioned and the finding of achlorhydria in some menopausal women.

[*May* 4, 1955]

DISCUSSION ON THE ENDOCRINE RESPONSE TO TRAUMA

Dr. Francis Moore (Surgeon-in-Chief, Peter Bent Brigham Hospital; Moseley Professor of Surgery, Harvard Medical School, Boston, Mass.):

Endocrine Response to Surgery

The central problem of surgical endocrinology concerns the relationship of the observed endocrine changes to the alterations in tissue metabolism which follow trauma. Our data point in a certain direction but are far from conclusive.

There is a considerable variety of metabolic patterns observed after injury. It is of interest that the differences between these metabolic patterns seem to be determined by the age and nutritional status of the patient, the degree of injury, the presence or absence of hæmorrhage, the nature of the anæsthesia and, most important of all, the actual details of the wound, be it primary clean soft tissue injury, burn, fracture or infected open wound.

Although the metabolic patterns are variable, most of those which follow extensive injury are associated with transient adrenal activation and show certain common denominators as follows: there is an initial period of bodily tissue destruction associated with early wound changes and lack of absorption of foodstuffs. This is followed by a "turning point", a phase in which the urinary nitrogen excretion rate is markedly restricted, the wound regains tensile strength and the ingestion of food is resumed. The patient then enters a long period of spontaneous protein anabolism during which muscular mass and strength is regained, and finally a period characterized by resumption of body fat. The metabolic variations concern the timing of these sequential phases, their intensity and, above all, the inter-relationships between fat, carbohydrate and protein metabolism on the one hand and water and electrolyte metabolism on the other.

The endocrine changes which occur during these phases of convalescence are much less clearly seen than the biochemical and metabolic changes; methods are uncertain and under constant evolution. It is these endocrine changes which concern us here even though their quantitative relation to tissue metabolism remains to be elucidated.

The Early Post-traumatic Phase

The description by Cannon (1915) of evidences for adrenal medullary activation by pain, fear and injury have been corroborated many times by clinical observation of injured patients. The two most potent stimuli seem to be fear and pain on the one hand and oligæmic shock on the other. Ether anæsthesia also appears to be a potent stimulus to the secretion of epinephrine and related compounds. The clinical manifestations of tachycardia, increased peripheral resistance and sweating have not as yet been correlated with direct chemical assay of adrenal medullary hormones in the blood and urine. These methods are rapidly evolving and in coming years we can expect to see more quantitative data in this area.

The peripheral wound stimulates centres in the hypothalamus which in turn stimulate the anterior pituitary to secrete ACTH. This activation chain has been studied by Hume (1953) and others. There is suggestive evidence that the peripheral wound may stimulate the central mechanisms both by neural and extraneural pathways. The increased blood ACTH concentration results in a sudden increase in the concentration of adrenal steroids in adrenal vein blood, in the peripheral blood and in the urine. Our methods of study have centred on the measurement of the free 17-hydroxycorticoids (17 OHs) in the blood and of the total 17 OHs in the urine. Previous studies in many laboratories have shown that the

changes in total 17-ketosteroids in the urine are variable and often inconsequential. Blood 17 OHs, however, increase rapidly with surgical trauma from normal concentrations in the range of 5 to 10 micrograms per cent to concentrations from 40 to 50 micrograms per cent. This increase occurs within six hours of making the incision and in most simple cases of elective civilian surgery the concentration is nearly normal again by the next morning. Ether anæsthesia alone produces increases to the range of 30 micrograms per cent. Non-shock-producing hæmorrhage in the normal volunteer apparently produces no significant rise in free blood 17 OHs. The free blood 17 OHs (largely compound F) are rapidly metabolized in the body following a variety of pathways. Some of the hormone is completely oxidized and appears as CO_2 (based on tracer study). Some of the hormone is reduced to tetrahydro-compounds. Some appears as 17-ketosteroids, and an amount estimated as about 30% appears in the urine as the conjugated 17 OHs. The normal urinary excretion in these substances ranges from 5 to 15 mg. per twenty-four hours. After intra-peritoneal surgery urinary excretion rises to the range of 30 to 40 mg. per twenty-four hours and remains from one to four days. In open long-bone fractures and in burns a higher peak may be reached (up to 50 mg. per twenty-four hours). Very minor traumata, such as herniorrhaphy, produce small but significant rises.

The blood eosinophil changes are loosely correlated with the steroid phenomena. The rising limb of the steroid curve correlates well with the fall in the eosinophils, and in simple clean soft tissue surgery the subsequent rise in eosinophils correlates rather well with the fall in steroid excretion. But in other settings the eosinophils may remain depressed for some days after the measurable steroid increases are passed.

The adrenalectomized subject maintained on constant doses of cortisone also shows eosinophil and metabolic changes closely resembling the normal pattern, as described by Dr. D. J. Ingle (Ingle *et al*, 1947; Ingle and Nezamis, 1950). Experiments carried out by Dr. R. W. Steenburg of our laboratories appear to demonstrate that in the adrenalectomized dog on constant doses of cortisone the blood level of 17 OHs rises with trauma. This suggests that trauma may alter the rate of inactivation or conjugation of the hormone. This is an interpretation supported by other evidence both in human and animal experiments, the details of which are beyond the scope of this brief discussion.

The initiation of increased nitrogen excretion rate correlates well with the increased steroid excretion, and in the first four days after trauma there is a good correlation between total steroid excretion and total nitrogen excretion. After this time the correlation is poor. We hypothesize that the steroid change helps to initiate a metabolic alteration but that the nature of the wound and the local events in the region of the wound, particularly as regards its stage of healing, are of controlling importance in the duration and intensity of this catabolic response.

Alterations in electrolyte metabolism are characteristic of injury. This may range all the way from massive accumulation of fluid in œdematous areas, burns or peritonitis, to the subtle changes in sodium excretion rate referred to as "sodium conservation". These latter changes may be initiated rapidly after trauma or they may not appear for a day or two. As a general rule, early appearance of sodium conservation is followed by early release. In older, more debilitated individuals, and especially in patients with heart disease, sodium conservation may persist for many days or weeks after trauma. This effect would appear to be mediated by aldosterone, but whether there is an increased secretion of aldosterone after trauma or whether the peripheral tissues merely react differently to constant levels has not as yet been established.

Alterations in water metabolism occur after major surgery and may be demonstrated to be distinct from the salt changes mentioned above (Le Quesne and Lewis, 1953). This change consists in a decreased tendency to excrete administered water loads, be they given by mouth or by vein. This evident antidiuresis may last only a day or two in well-nourished people but in individuals who are cachectic or suffering from disease of heart, liver or kidneys, this antidiuretic tendency is accentuated and prolonged. The recent demonstration of increased amounts of an antidiuretic substance in the urine of surgical patients (Lewis) suggests that this change in water metabolism is mediated by a humoral substance but the positive identification of increased posterior pituitary activity is, to our knowledge, still lacking.

The Period of Metabolic Reversal

After this initial phase of endocrine activity the patient passes through a period in which there is a clinical "turning point"; appetite becomes more manifest, there is a marked decrease in urinary nitrogen excretion and evidences of adreno-cortical activity become minimal. This phase is very clear-cut in extensive intra-abdominal surgery. In other settings, particularly with bony injury, burns or sepsis, the close correlation between metabolic events and decreased steroid activity is lacking. Whether or not this endocrine

correlation is clearly seen, normal convalescence is characterized by a period of markedly decreased urinary nitrogen excretion which then passes on to anabolism, and it is this event which has given rise to the concept of the "corticoid withdrawal phase". It is a period when metabolism resembles that of corticoid withdrawal after short-term high dose administration.

The occurrence of salt diuresis is sometimes seen in this period but with increasing numbers of observations we are impressed with the variability in time of salt changes. We have now observed several patients who have shown clear-cut reduction in nitrogen excretion rate while still actively conserving sodium.

The rise and "overswing" of the eosinophils may occur at this time but it is also irregular.

Despite these variabilities in relationship, the nitrogen reduction is an inevitable prelude to anabolism, and we have never seen it occur in the face of maintained high steroidal activity: steroid reduction is essential for its occurrence, whether or not its cause.

The Period of Anabolism and Regrowth

Prolonged nitrogen anabolic activity resulting in increased strength and muscle mass is a characteristic feature of surgical convalescence. After clean primary soft tissue surgery this occurs after the fifth to seventh day when the nitrogen excretion reduction occurs. This anabolism can only occur in the presence of a normal dietary intake of nitrogen and calories.

The endocrine setting for this anabolism appears to be one of minimal adrenal steroid activity of the 17 OH type. The 17-ketosteroid excretion is also low. Whether a "growth hormone" of pituitary origin or some as yet unknown anabolic principle of adrenal or gonadal origin is the driving force we cannot say. There are many remarkable metabolic features of this anabolism, particularly its rate and duration. But its endocrine activation is not clear at present.

Unfortunately the same must be said for the resumption of body fat or anhydrous weight gain which commences late in convalescence and outlasts the other metabolic features. Its metabolic characteristics are well known but not its endocrine mediation. Like protein anabolism, it also requires an adequate diet.

Summary

In summary, then, we may conceive of surgical convalescence as driven by an endocrine engine. The convalescent metabolism has been described but the endocrine forces are less well understood and the precise mechanism by which they produce the tissue changes is unknown.

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Professor G. M. Wilson (Department of Pharmacology and Therapeutics, University of Sheffield):

The work that I am reporting was done in collaboration with Professor R. P. Jepson at the Sheffield Royal Infirmary. Our efforts have been directed to the study of two different aspects of endocrine function following surgical operations. Firstly, we have been interested in the serum electrolyte changes which develop after operation and their relation to the action of antidiuretic hormone and water retention. Secondly, we have studied the metabolic changes following bilateral adrenalectomy with the patient kept on a constant dose of cortisone.

Serum electrolyte changes.—Previous observations have shown that following major surgery the serum sodium and chloride concentrations are often depressed below the pre-operative level for several days (Moore and Ball, 1952; MacPhee, 1953). This change may be extremely conspicuous in those undergoing cardiac surgery and may be accompanied by a rise in the serum potassium concentration (Wilson *et al.*, 1954). It was also noted in these cases that the fall in serum sodium and chloride concentrations was greater in those having a larger water intake in the post-operative period. There is considerable evidence that a powerful antidiuretic factor is at work in the immediate post-operative period and this may lead to considerable water retention if fluid is given freely (Wynn and Rob, 1954). We have attempted to assess the extent to which the fall in serum concentrations of sodium and chloride after partial gastrectomy may be attributed to dilution

brought about in this way. Changes in serum sodium and chloride concentrations were followed closely before and during the first two days after operation. If no fluid was given either by mouth or intravenously for the twenty-four hours following operation no fall in the electrolyte concentrations occurred, but considerable dehydration resulted. As soon as some fluid was given the fall began, even though the amount was quite insufficient to correct the dehydration. In patients given only small amounts of fluid at operation, insufficient to cause any overhydration, the concentrations fell immediately. The results of these observations indicated that the decreases in electrolyte concentrations could not be attributed solely to post-operative water retention brought about by the release of anti-diuretic hormone. In normal subjects administration of posterior pituitary extract only causes a fall in serum electrolyte levels if it is given with a considerable excess of fluid. On the other hand, the post-operative fall may develop without any fluid excess, but is always more conspicuous when the fluid intake exceeds the output. The exact mechanism of the electrolyte changes occurring after operation remains obscure.

Adrenalectomy and constant cortisone dosage.—The relationship of the activity of the adrenal cortex to the metabolic changes that occur after a major surgical operation is still uncertain. It is known that the blood levels of hydroxycorticoids and the urinary excretion of steroid end-products rise post-operatively (Sandberg *et al.*, 1954; Venning *et al.*, 1944), but these changes do not necessarily reflect an increased secretion of steroids by the adrenal cortex. In the adrenalectomized animal maintained on a constant dose of cortisone, the typical response still develops after an injury (Ingle, 1952). The operation of bilateral adrenalectomy for the relief of metastatic carcinoma affords an opportunity of studying the problem in man. In our observations we have given a constant dose of cortisone, either 100 mg. or 150 mg./day, beginning several days before operation and continuing with this dose on the day of operation and for the succeeding ten days. On such a regime the eosinophil count regularly falls to zero immediately after operation but subsequently rises, often to high levels, and then falls to about the pre-operative level. After bilateral adrenalectomy a transient fall in serum concentrations of sodium and chloride, an enhanced rate of nitrogen excretion and retention of sodium and chloride all occurred. An increase in the rate of excretion of 17 ketogenic steroids as measured by the method of Norymberski and his associates (1953) appeared for two or three days after operation in some patients. These are all changes identical with those seen after major abdominal surgery in a patient with intact adrenal glands.

One difficulty in the interpretation of these observations is that the adrenals may well produce an excess of secretion during the time between induction of anæsthesia and completion of removal of the glands. The pre-operative administration of large doses of hormone probably diminishes greatly adrenal secretion, but the extent and completeness of this suppression cannot readily be measured. Some of the immediate post-operative changes may possibly be attributed to adrenal stimulation but the later metabolic features clearly cannot be due to changing rates of supply of adrenal cortical hormones. The exact role of the adrenal cortex is still undetermined but it is becoming clear that a change in its rate of secretion is not the main factor in initiating and sustaining the metabolic response to an injury. Other mechanisms, as yet undefined, are apparently at work.

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Mr. L. P. Le Quesne (Department of Surgical Studies, Middlesex Hospital, London):

Professor Wilson has commented on the alterations in plasma electrolyte concentration which follow operation, and on the importance of recognizing and interpreting these changes correctly. There are similar changes in the urine. For some thirty-six hours after operation there is necessarily a low urine output of raised specific gravity, and for several days after operation there is a diminished concentration of salt in the urine. These changes are a reflection of the post-operative metabolic disturbance, and must not be taken as indications to increase the water and/or salt intake. In the past there has been a tendency to take these isolated findings as evidence, in themselves, of a depletion of water or salt, but the inquiry should be taken one step further back, so that the critical questions become: Why are this patient's kidneys conserving salt, or conserving water? Is it because

the patient is short of these substances, or are these changes just a reflection of the patient's metabolic response to surgery ?

It is of interest to note how, in the last few years, it has become apparent that factors other than the increased secretion of adrenocortical hormones may be responsible in part for the metabolic response following operation. We now know that the antidiuretic hormone plays some part in this response, and it may well be that there are further, as yet unidentified, factors at work. These changes could be studied much more easily if there were available a simple method of giving patients a constant, palatable intake by mouth, so that metabolic studies could be carried on for many days after operation, without the complexities introduced by a varying intake or the unpleasantness of tube-feeding.

Dr. A. Stuart Mason:

I wish to illustrate one aspect of this problem from data obtained on patients undergoing total hypophysectomy or adrenalectomy for alleviation of carcinomatosis. Fig. 1 shows the effect of total hypophysectomy on salt and potassium balances when the patient was maintained throughout on a constant dose of corticotrophin (60 mg. daily) and a constant salt intake. Post-operative salt retention was followed by a period of salt loss, as in a normal subject undergoing surgery. Similar results are shown in Fig. 2 which illustrates the

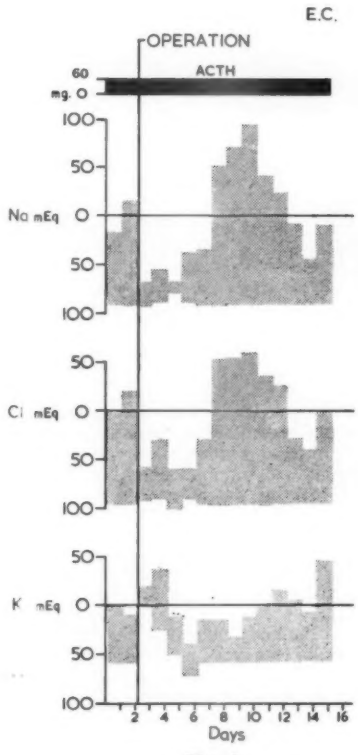

FIG. 1.

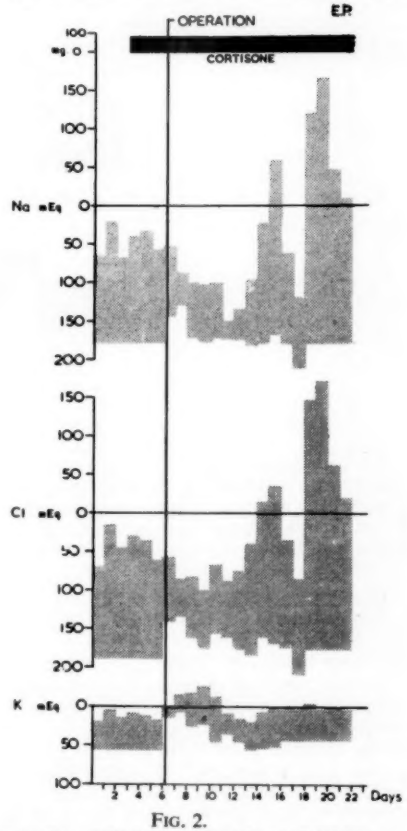

FIG. 2.

In Figs. 1, 2 and 3 the data are charted according to the method of Reifenstein *et al.* (1945).

effect of total adrenalectomy on electrolyte balance when the patient is maintained throughout on a constant dose of cortisone (80 mg. daily) and constant salt intake. In this instance the overall balance indicated salt retention, although the immediate post-operative retention was considerably greater than in the succeeding period. The salt intake was high throughout, and experience with other cases had indicated that the amount of salt

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intake and hormone administered will influence the degree of retention. Further studies on this patient (Fig. 3) showed a considerable post-operative nitrogen loss with eventual return to equilibrium, with concomitant changes in phosphorus and calcium balance.

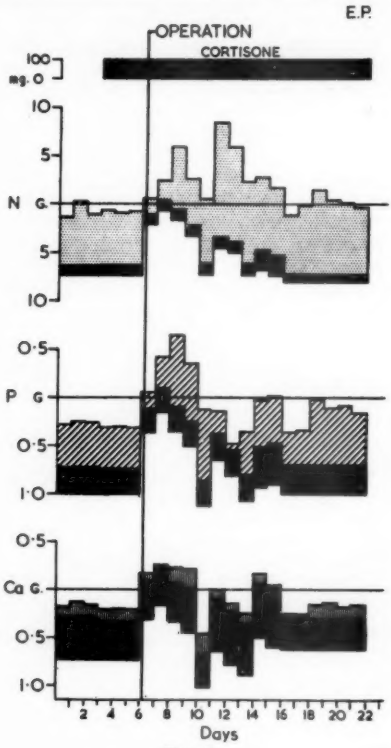

FIG. 3.

In both patients the metabolic response to trauma was similar to that found after operations on patients with normal adrenals. The results indicate that these alterations of metabolism are not directly related to variations in adrenal hormone output, and that tissue factors play an important part in the body response to trauma. The data obtained supported Ingle's concept (1952) of the "permissive" role of the adrenal.

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Professor Charles H. Gray:

In the interpretation of analyses of adrenal steroids in the body fluids it is very important to remember that by the existing chemical techniques only a very small number of the steroids secreted by the adrenal cortex are estimated. There is evidence that the adrenal cortex secretes at least five different hormones. Each of these hormones may be changed in the body to a variety of metabolites which may be excreted in the urine either in the free form or conjugated with glucuronic acid or sulphuric acid. The resulting complex mixture of these metabolites in the urine renders assessment of adrenal function by simple estimations an extremely complicated procedure. The adrenal cortical steroids and their metabolites may be classified into androgens, carbohydrate active steroids, and mineralocorticoids active in inducing retention of sodium and excretion of potassium. In addition some compounds derived from the adrenal cortical steroids are inactive. It is not surprising therefore, that existing chemical methods of investigation are inadequate. It seems not impossible that the anabolic and catabolic changes following trauma may be due to the secretion by the adrenal cortex of different proportions of these substances.

Section of Urology

President—VICTOR W. DIX, F.R.C.S.

[*March* 24, 1955]

An Aid to Aortography

By W. BARR STIRLING, M.B., F.R.F.P.S., F.R.C.S.Ed.

THE value of translumbar aortography, originally described by Dos Santos *et al.* (1929) is now established. It is not the purpose of this paper to discuss the conditions, urological and non-urological, in which it may prove useful, but rather to relate some of my experiences and suggest a simple method of rapid injection.

Following the first British report on aortography by Griffiths (1950) I adopted the technique which he described. For various reasons the results proved disappointing and in some instances no information at all was gained.

Several factors may influence the production of good aortograms. The technique of puncture requires no further description but the position of the needle within the aorta is important. Unless it is well and truly within the lumen, no satisfactory picture will be obtained. This is obvious and requires no further comment, except that the level of puncture is not so important as was previously thought.

The X-ray factors will depend to some extent on the machine available. Originally I used the technique which Griffiths described of a wooden tunnel and stationary grid. In this method several cassettes are loaded into the tunnel and may be withdrawn quickly allowing films to be taken at intervals of about two seconds. I was not satisfied with the quality of picture so obtained and have returned to the usual X-ray table and Potter-Bucky diaphragm. I am convinced that one good arteriogram and one or two nephrograms are much more valuable than more films of either phase, of poorer quality and definition. Cassettes can be changed on the Bucky at intervals of four seconds so that one immediate film already in position can be obtained and the second picture four seconds later corresponds to the maximum concentration of the nephrogram. A third film at eight seconds will cover any delay.

Certainly in peripheral arteriography faster films are desirable and the use of some form of seriograph may be helpful. In urology, I have not been impressed by the results of such machines. In practice it is a simple matter in peripheral arteriography to repeat the injection and take films in the intervals between the previous ones, thus obtaining pictures every two seconds. Until really efficient cine-radiography or fast photography (five to ten films per second) is available, I prefer to carry on with my simple technique.

Elaborate radiographic equipment is not necessary, and I carry out the examination in the Urological Outpatient Clinic. The usual X-ray factors used are: 72 kV, 200 mA, 0·2 sec. at 40 in., anode film distance. The Bucky setting between one-half and one-third of a second.

The question of the medium is also important as tragedies have been reported following the use of certain dyes. For the past two years, I have used sodium acetrizoate, largely the American preparation Urokon 70% (Mallinckrodt), and more recently its British equivalent, Diaginol 70% (May & Baker). This drug is less toxic, more rapidly eliminated and denser than any other and I have had no trouble with it at all. I consider, however, that an intravenous test dose should be given in every case and reliance should not be placed on a previous uneventful excretion urogram in which a different drug and concentration may well have been used.

The most important factor, undoubtedly, is the rate of injection. The slow rate due to hand injection in the original technique used, was, I am quite sure, responsible for the poor results. The quicker the delivery, the greater the concentration of the dye in the aorta, and the greater the concentration, the more detailed the picture of the aorta and its branches. I had the privilege of discussing this with Dos Santos, some months ago, when he delivered the Macewen Memorial Lecture in Glasgow University. He agreed that the secret of good aortography lies in rapid injection.

In an attempt to increase the delivery rate by hand pressure I tried various types and sizes of syringe and attachments. None of these made much difference, and I could not inject 20 ml. through an 18 S.W.G. needle in less than 6 seconds or through a 16 S.W.G. needle in less than 3–4 seconds. Eventually after a syringe broke and I got the plunger into my hand I was convinced that some other method of injecting the dye was necessary.

There were already in existence two types of apparatus for rapid injection.

The first, originally described by Dos Santos, consisted of the use of compressed air or oxygen. This did not appeal to me as it seemed to have two drawbacks. Any slight technical defect or a human error in manipulation might result in a tragedy. In the second place there is little control and no tactile perception. The second type consisted of the use

of a spring acting on the plunger as advocated by Melick and Vitt (1948). I question if this is very effective, and it also has little control and no perception.

It seemed to me that what was required was some form of lever action under manual control. The mechanical advantage of vertical lever action is considerable, so I had constructed in the hospital an instrument embodying this simple principle. The success of this was astonishing and the instrument, which has been modified slightly, is now in the hands of the instrument makers (Chas. F. Thackray Ltd., Leeds).

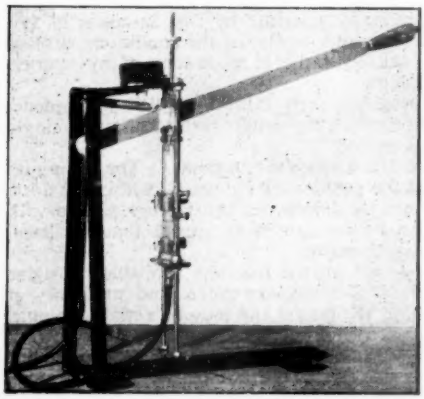

FIG. 1.—"Injector" for rapid introduction of opaque medium.

The apparatus is all metal (*see* Fig. 1). There is a heavy base to provide stability. The supports at the end are transfixed by a spindle on which the lever is hinged. The spring serves to keep the lever in the "up" position and to provide some tension. The vertical rods farther back are threaded and carry a platform on which the shoulders of the syringe rest. The clips which are removable are hinged and tightened by a butterfly screw. The clips and platform are adjustable, the latter on the threaded vertical rods so that different sizes of syringe may be used, for example, a 50 ml. syringe for angiocardiography. The lever passes through the slot in the vertical metal plate, which slides on the rods and the cup-shape attachment depresses the plunger. In order to prevent the plunger going too far and shattering the syringe, the vertical rod at the top is threaded and has an adjustable metal ring, so that a known quantity of dye may be injected.

In order to eliminate entirely any error or delay in the co-ordination between radiographer and operator, a simple electrical contact switch, which is connected to the X-ray machine, is placed on top of the instrument. This is activated by the screw stopper so that an immediate picture is taken when a known quantity of medium has been injected in a known time.

The syringe and tubing filled with the dye are placed on the platform by sliding the nozzle through the slot. The clips are then closed, the top one gripping the rim at the top of the barrel. The lower clip serves only to steady the syringe and maintain it in the true vertical. In the original model these clips were made to grip the barrel tightly, but this was found to increase the resistance considerably—a fact which I had not appreciated to begin with, but which is easily proved by grasping an all-glass syringe.

As considerable pressure is used, it is essential to have good fittings and pressure tubing. I have found the Luer-Lok type of mount on a 20 ml. all-glass syringe to be the most satisfactory. The best tubing was that recommended to me by Mr. I. H. Griffiths—this has an additional cotton woven sheath like the tubing of a bicycle pump. Ordinary pressure tubing tends to "balloon" after repeated autoclaving, and I have not found the modern plastic types to be entirely satisfactory.

As regards technique, I have discarded the use of a three-way adaptor and saline perfusion as the technique very seldom requires a second injection. The needle is inserted and when it is judged to be in the correct position the tubing is connected, rapid injection made and the needle withdrawn. I aim to inject 15–18 *ml. in not more than one second* but the quantity and time are both under complete control of the operator.

Having devised a suitable instrument which produced highly satisfactory pictures, I was interested in the effects of rapid injection.

The injection of 20 ml. in 0·75 sec. through a 16 S.W.G. needle requires a pressure of 800 mm.Hg. A similar injection through an 18 S.W.G. needle requires 900 mm.Hg. The same injection, by hand, records on the manometer a pressure of 500 mm.Hg over 4 seconds for a 16 S.W.G. and 600 mm.Hg over 6 seconds for an 18 S.W.G. needle. Is the greater pressure dangerous?

Two factors come into play. First the effect of a thin jet of fluid forcibly projected against the aortic wall. The injection of 20 ml. of fluid through a 16 S.W.G. needle which has an internal diameter of 1 mm. in one second produces a muzzle velocity of 2,000 cm. per second—this is twenty times the normal velocity of the blood in the aorta. Velocity falls rapidly from the muzzle onwards and when this fluid is injected across another heavier fluid such as blood with its own velocity, against it at an angle of 45 degrees the fall

immense. It was not possible to calculate the effect mathematically so the following experiments were carried out:

Fresh aortas were obtained from the post-mortem room and injections were made both in the normal tubular form and with the aorta opened and pinned out. These injections were made at varying distances from 1·0 mm. upwards from the aortic wall, both across air and across fluid—the latter being Darrow's solution. Serial sections both in the vertical and transverse planes were cut of the various target areas. In no case could any damage to the intima be seen on histological examination.

The second factor is the rise of pressure within the aorta during injection on the living patient. Again it is quite impossible to calculate this. Experiments were therefore carried out in which two needles were inserted into the aorta 2 cm. apart.

Injections were made through the upper needle and readings taken from the lower needle which was connected to a manometer. Further recordings were made through the upper needle, the lower one being used for injecting the medium.

Originally a simple water manometer was used, but this may not be entirely reliable so subsequent readings were taken on a sensitive accurate electromanometer. In no case did the rise of intra-aortic pressure exceed 8 mm.Hg.

A further experiment to determine the pressure transmitted to the renal artery was carried out. It is impossible to carry out a deliberate blind puncture of a renal artery and it did not seem justifiable to do this at operation unless the kidney required removal. Accordingly a patient in whom left nephrectomy was necessary was selected. At operation I inserted a needle into the left renal artery so that the point lay almost at its junction with the aorta. A second needle was inserted into the aorta under vision with the point directed downwards 1 cm. above the first one and the usual injection made. The rise of pressure recorded on the manometer from the renal needle was 2 mm.Hg. These rises of intra-aortic pressure seem quite insignificant.

In some cases there is a considerable retrograde spread of the dye up the aorta. In order to ascertain whether this has any effect on the cardiac output or cycle, electrocardiographic

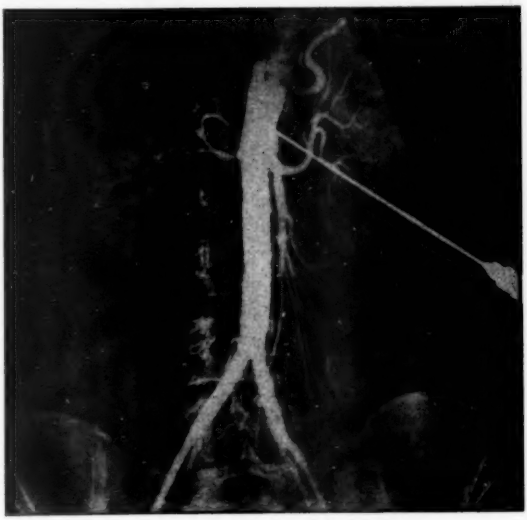

FIG. 2 (*Case I*).—Normal aortogram.

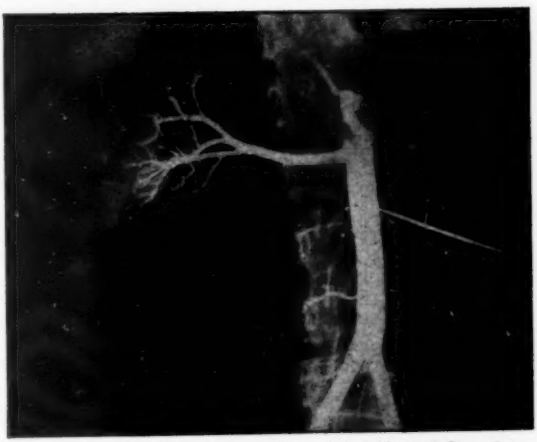

FIG. 3 (*Case II*).—Vascular supply to right kidney (left nephrectomy). Needle inserted below origin of renal arteries.

tracings were carried out during injection. No alteration in the tracings has been found. These experiments suggest that rapid injection such as this is safe.

Two criticisms, however, may be made.

Rapid injection may lead to the filling of more vessels than those desired. Should this occur, however, the clarity of the picture is such that it more than compensates for any overlay and I have had no difficulty in the interpretation of such films. The insertion of the needle at the point of election between the superior mesenteric and the renal arteries cannot, as I have found in anatomical dissection and in aortography, be done with accuracy in every case. Rapid injection such as this will outline the renal arteries even where the needle is inserted below them (*see* Figs. 3 and 4). Further, in cases of ectopia or other congenital anomaly the number and origin of the arteries are both unknown and good aortic filling is necessary to show them.

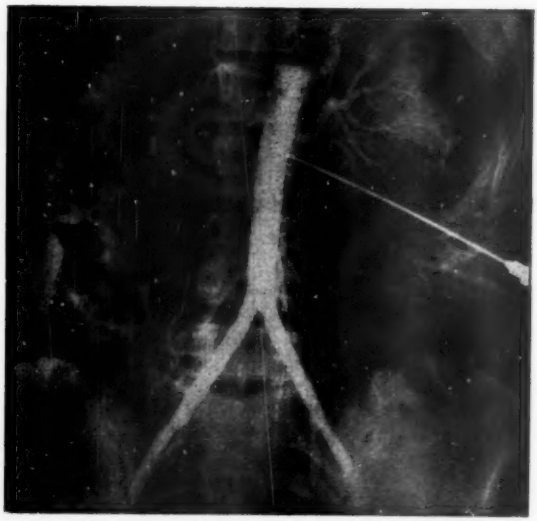

FIG. 4 (*Case III*).—Vascular supply to left kidney. Note stump of right renal artery. Needle inserted below origin of renal arteries.

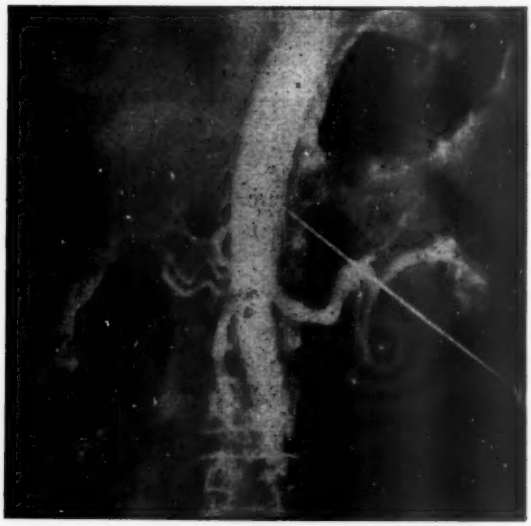

FIG. 5 (*Case IV*).—Classical appearance of vascular parenchymal neoplasm of left kidney.

There remains the vexed question of injection into one renal artery. I do not deny the potential danger of such an event, either by rapid injection or by hand injection. In an attempt to obviate this I had made for me two needles of different design. Each had the end blocked and one of them had a long lateral opening, the other, four smaller lateral openings so that the dye would be injected vertically up and down the aorta. In spite of these openings having a greater surface area than the end of the usual needle the resistance was very much greater. In practice they did not prove very satisfactory—the main difficulty being in determining their position and the risk of extravasation seemed greater. I have therefore, for the present, reverted to the usual type of needle.

Personally I have had no trouble so far and feel that the dangers of rapid injection are exaggerated, provided the pressure is not excessive. To me the type and quantity of the dye are just as important. I have injected most of the dye into the cœliac axis and into one renal artery without the slightest ill-effect. For those, however, who feel apprehensive about this there remains the test injection to determine the exact position of the needle.

(Numerous slides were shown to illustrate the type of picture obtained by this technique.)

The following five examples are quoted:

Case I (Fig. 2).—Female, aged 34. Diagnosis of coarctation of abdominal aorta made elsewhere at laparotomy. The aortogram is normal in all respects and the renal and some other branches clearly defined. 18 ml. dye injected in 1 sec. through a 16 S.W.G. needle at level of L.1.

Case II (Fig. 3).—Female, aged 49. Small stone in lower pole of right kidney. Left nephrectomy for stone, 1940. Aortogram shows vascular supply to the right kidney. Slight irregularity on the opposite side denotes the stump of the left renal artery. 16 ml. dye in 0·75 sec. through a 16 S.W.G. needle. Note that the needle is inserted well below the origin of the renal artery.

Case III (Fig. 4).—Female, aged 27. Stone in right ureter. No excretion right kidney on I.V.P. Dye failed to enter kidney on ascending urogram. Ureterolithotomy performed. Post-operative I.V.P. and ascending urogram again failed to demonstrate right kidney. The aortogram shows vascular obliteration of the right renal artery, only a tapering stump remaining. Left renal vascular distribution normal. Small right atrophic kidney removed at operation. 18 ml. dye in 1 sec. through 16 S.W.G, needle inserted below origin of renal arteries.

These two cases illustrate the point made earlier that the level of puncture is not so important with this technique as it is with hand injection.

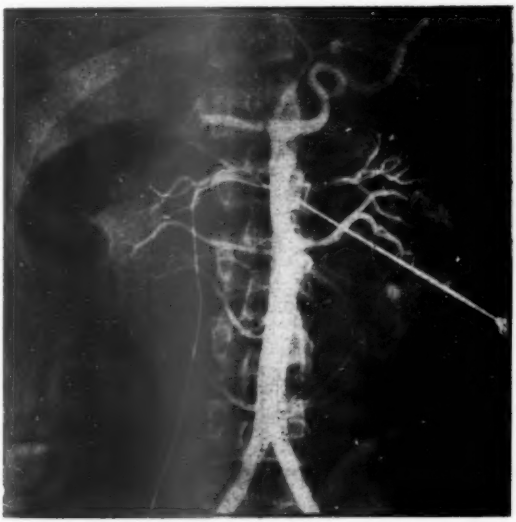

FIG. 6 (*Case V*).—Bilateral incomplete renal rotation with calculus in lower pole of left kidney. Extensive renal vascular supply demonstrated by filling of aorta.

Case IV (Fig. 5).—Female, aged 68. The aortogram illustrates the classical picture of a renal adenocarcinoma. Hypertrophy of left renal artery due to increased blood supply. Displacement of main branches and "pooling" of dye in the vascular sinuses. 16 ml. dye in 0·75 sec. through a 16 S.W.G. needle inserted at T. 12.

Case V (Fig. 6).—Male, aged 24. Calculus in lower pole of left kidney. Bilateral incomplete rotation, not horseshoe kidney. The aortogram shows four renal arteries on the right side and three arteries to the left kidney. Note also right spermatic artery. 18 ml. dye in 1 sec. through a 16 S.W.G. needle at L.1.

In order to demonstrate the extensive renal blood supply in such cases it is essential to outline the major part of the abdominal aorta at one time. Rapid injection is necessary to achieve this.

This apparatus has now been used in more than 100 cases in patients between the ages of 14 and 76. There has been no morbidity in any patient or damage to any syringe.

I feel that rapid injection by this technique is quite reasonably safe for the patient, safer for the operator and produces pictures of a quality far superior to those obtainable by hand injection.

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Ionic Migration Across the Mucosa of the Small Intestine and Its Significance in Urology

By A. D. CARE, M.A., Ph.D.

Department of Urology, University of Leeds

AN isolated loop of ileum has been used for various urological procedures; these include the use of a coil of ileum to enlarge a contracted bladder, to replace an excised portion of ureter, to relieve simultaneously a contracted bladder and a hydronephrosis of a sole remaining kidney, to act as an artificial bladder and also to reimplant into the bladder ureters previously transplanted into the colon.

Although no electrolyte imbalance has been noticed in our unit at Leeds (Pyrah *et al.*, 1955) following these operations, and having established, as we believe, the technical soundness and practicability of these procedures, it was thought desirable to undertake a study of the ionic exchanges which may take place across the mucosa of the ileum when urine is in contact with it. This study seemed all the more desirable in view of the known absorption of electrolytes, frequently resulting in an electrolyte imbalance in the internal environment, when urine is present in the large intestine following uretero-colic anastomosis. Moreover, Bricker (1950), Wilson (1953) and Annis *et al.* (1954) have all recorded instances of hyperchloræmic acidosis after implantation of the ureters into an ileal loop, though these instances may have a purely mechanical interpretation. Tasker (1953) has reported a case in which death from hyperkalæmia was believed to have resulted from potassium absorption following the operation of ileo-cystoplasty, which was complicated by oliguria and hence by the subsequent failure of potassium elimination.

Since the movements of sodium, chloride and potassium ions have the greatest bearing upon the incidence of chemical imbalance, it was decided to study these movements first. This was done in two ways. As an example of the first, a fluid containing electrolytes having a known composition approximating to that of urine, was introduced into an excluded bladder where it was allowed to remain for one hour. It was removed and analysed and the two sets of figures were compared. This experiment was then repeated after an isolated coil of ileum had been added to the bladder in order to increase its capacity. In this case allowance had to be made for the urine which flowed into the new bladder from the attached ureter. This investigation, by simple chemical analysis, will give only the *net* changes in the ions which are analysed but will give little or no information about the *actual movements* of these ions which have occurred.

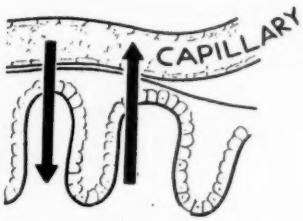

FIG. 1.—The simultaneous migration of ions between ileum and blood in both directions resulting in the establishment of a dynamic equilibrium.

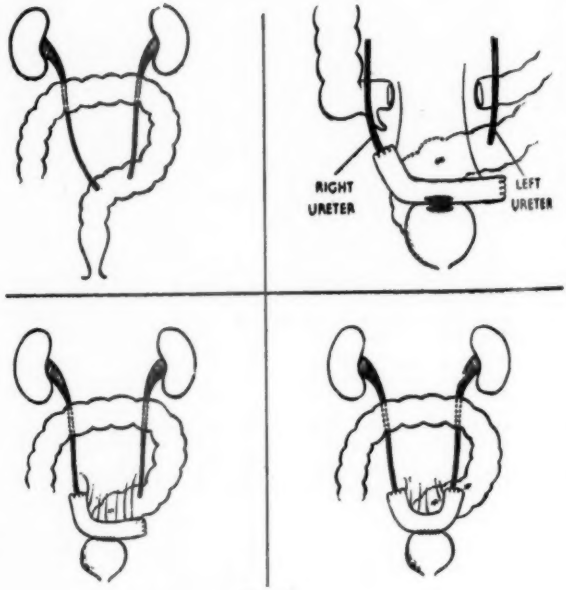

FIG. 2.—The use of a loop of ileum for the reimplantation of the ureters from the sigmoid colon into the bladder.

FIG. 2.

The second method involved the use of radioisotopes and it was then possible to gain information about the quantitative ionic movement between the organ and the blood stream in either direction. In this study we used the radioisotopes Na^{24}, Cl^{38}, and K^{42}. Sodium, chloride and potassium ions are known to be in a continuous state of movement across the mucous membrane of the intestine and the closely applied capillary walls in both directions at the same time, thus resulting in a transport of ions *from* the lumen of the gut *to* the blood plasma, and *from* the blood plasma *to* the lumen of the gut (Fig. 1). But this transport of ions in both directions at the same time is not necessarily equal, the direction of net transport of the given ion at any one time depending upon various factors. There is ultimately reached an equilibrium between the concentrations of ions at the two sides of the

membrane, varying for different ionic concentrations, which is called a *dynamic equilibrium* (Visscher *et al.*, 1944).

The first case in which we applied these techniques to the study of ionic migration across the wall of the ileum was a case of *uretero-ileocystoplasty*.

The patient was a woman aged 42 with a very large vesico-vaginal fistula for which both ureters were transplanted into the distal colon. Recurrent attacks of severe ascending renal infection developed in the succeeding twenty months, resulting in a considerable degree of invalidism. As it was observed that the fistula in the now empty bladder had markedly reduced in size, it was decided to repair the fistula in order to obviate further damage to the kidneys. The ureters were then reimplanted into the bladder, employing an isolated coil of ileum (Fig. 2) because the ureters would not reach from their point of section at the sigmoid anastomosis to the bladder. When the bladder had been repaired and was seen to be firmly healed, and before the ureters were reimplanted into the bladder, the patient had a completely healed and excluded bladder which could be examined for possible migration of sodium and chloride ions across its mucosa into the blood stream. In this way, a control was obtained for studies on the effects of the addition of an ileal loop to the bladder, on the ionic migration between this modified bladder and the blood.

It was first necessary to study the significance of any given level of radioisotope *concentration* in the blood stream, as measured by Geiger-counter techniques, starting from the moment of its injection and for a given subsequent period.

If exactly equivalent amounts of sodium and chloride ions were injected intravenously at the same time, then the concentrations in the blood would gradually become different because these ions have different volumes of distribution in the body and, moreover, move into these volumes at different rates. When intravenous injection of the two isotopes Na^{24} and Cl^{38}, was given and the concentrations of these isotopes in the blood were measured, with time, the graph shown in Fig. 3 was obtained. From these curves it was possible to

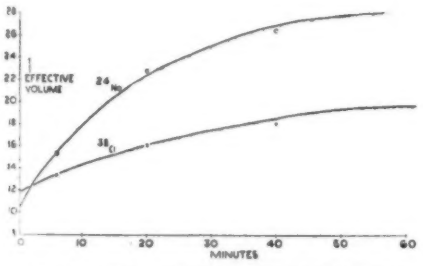

FIG. 3.—The relationship between the effective volumes of dilution and the time after an intravenous injection of Na^{24} and Cl^{38} ions.

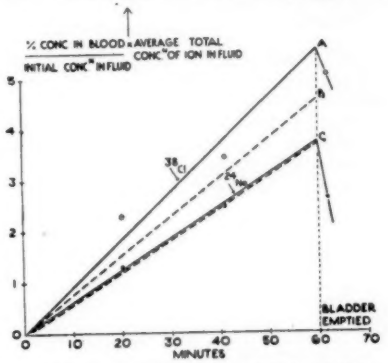

FIG. 4.—The absorption of Na^{24} and Cl^{38} ions from an excluded bladder (the ureters having been transplanted into the colon) and the subsequent uptakes of these ions by the blood. The ordinates are expressed in mEq./l. AB represents the true differential uptake after 60 minutes of Cl^{38} ions relative to that of Na^{24}, expressed in mEq./l.

calculate mathematically (Reed and Care, 1954) the *theoretical* blood uptake *v.* time curves of Na^{24} and Cl^{38}, which *would* arise if sodium and chloride ions migrated across a given membrane in the body, or across the wall of a body (in our case the ileum), *in exactly equivalent amounts* expressed in mEq./l. These *theoretical* uptake curves could then be compared with the *actual* uptake curves in order to detect any departure from an uptake of sodium and chloride ions in amounts equivalent to one another.

Having thus established the foundations for the investigation, the technique was to introduce into the bladder 100 ml. of an artificial urine (Table I) labelled with the radioisotopes Na^{24} and Cl^{38} (half-lives 15 hours and 38 mins. respectively) and to observe the movement of these isotopes from the bladder into the blood over the 60-minute period during which the fluid was retained in the bladder. This was done by taking blood samples at suitable intervals and measuring their radioactivity by Geiger-counter techniques. The

decay of the radioactivity of these blood samples, with time, was measured, and the proportions of Na^{24} and Cl^{38} in mEq./l. were calculated by taking advantage of their very different half-lives. Fig. 4 shows the uptake into the blood of Na^{24} and Cl^{38} ions in mEq./l. from the excluded bladder. The uptakes are very small and they indicate the existence of a very small exchange of sodium and chloride ions, between bladder contents and the blood, not greater, in fact, than four to five milliequivalents in the 60 minutes of the experiment. Moreover, the amounts of sodium and chloride ions, so taken up, are approximately equal. When the observed uptake curves OC and OA are fitted to the theoretical curves of uptake OC and OB, which are calculated on the assumption that Na^{24} and Cl^{38} have been taken up in exactly equivalent amounts, it is seen that Cl^{38} is taken up to a slightly greater extent than Na^{24} but this difference is not significant. We believe that this is the first time that the observation has been made that these ions can cross the mucosa of an isolated bladder into the blood stream.

The chemical analyses of the fluid used before and after its retention in the excluded bladder are shown in Table II; within the limits of experimental error there appears to be

TABLE I.—M. D., FEMALE. THE COMPOSITION OF THE ARTIFICIAL URINE USED

	Grams/litre
Sodium	1·9
Chloride	2·8
Urea	13·4
Sulphuric acid	2·45
Ammonium bicarbonate	1·94
Potassium dihydrogen orthophosphate monohydrate	3·49
Creatinine	1·00
Hydrated magnesium sulphate ..	1·50
Calcium lactate	1·11

TABLE II.—THE COMPOSITION OF AN ARTIFICIAL URINE BEFORE AND AFTER RETENTION IN AN EXCLUDED BLADDER

		Before retention	After retention
Time	min.	0	60
Volume	ml.	100	93
Cl	mEq.	7·86	7·52
Na	mEq.	8·40	8·07
K	mEq.	2·55	2·44
Urea	mg.	820	642

no significant *net* ionic movement across the bladder wall, despite the fact that small amounts of Na^{24} and Cl^{38} ions were shown by the previous experiment to move across the bladder epithelium into the blood. Equivalent amounts *must* therefore have migrated in the opposite direction, i.e. from blood to bladder, in order to give the zero net transfer shown chemically. A dynamic equilibrium is thus shown to exist.

The above procedure was repeated after one ureter had been reconnected to the bladder by means of the ileal loop. Fig. 5 shows the uptake into the blood of Na^{24} and Cl^{38} ions in

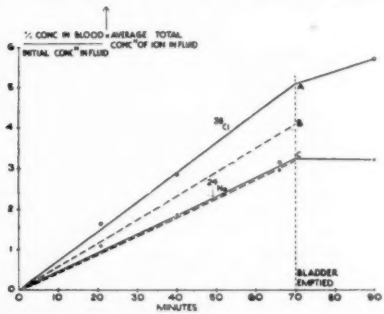

FIG. 5.—The absorption of Na^{24} and Cl^{38} ions from a bladder with attached ileal loop to which one ureter has been anastomosed, and the subsequent uptakes of these ions by the blood. The ordinates are expressed in mEq./l. AB represents the true differential uptake after 70 minutes of Cl^{38} ions relative to that of Na^{24}, expressed in mEq./l.

mEq./l. from this modified bladder. After the theoretical and experimental sodium curves OC have been fitted together, it is seen that the theoretical and experimental chloride curves (OB and OA respectively) are again almost coincident, i.e. the fact that AB is very small is indicative that sodium and chloride ions move in the direction, bladder plus ileum to blood, in almost equivalent amounts.

To verify this finding, the fractional losses of Na^{24} and Cl^{38} from the fluid in the bladder plus ileal loop were calculated, corrected for isotopic dilution and compared (Table III).

TABLE III.—COMPARISON BETWEEN THE FRACTIONAL LOSS OF Cl^{38} AND Na^{24} IONS FROM A BLADDER ENLARGED BY A LOOP OF ILEUM. THE LOSSES ARE CORRECTED FOR ISOTOPIC DILUTION (M. D.

$$\frac{\text{Fall in concn. of } Cl^{38} \text{ ions}}{\text{Initial concn. of } Cl^{38} \text{ ions}} \times \text{Av. concn. of } Cl^{-} \text{ ions in bladder fluid in mEq./l.} = 6{\cdot}05 \text{ mEq./l.}$$

$$\frac{\text{Fall in concn. of } Na^{24} \text{ ions}}{\text{Initial concn. of } Na^{24} \text{ ions}} \times \text{Av. concn. of } Na^{+} \text{ ions in bladder fluid in mEq./l.} = 6{\cdot}95 \text{ mEq./l.}$$

The close agreement between these two values is indicative of the equivalence with which sodium and chloride ions migrate across the ileal mucosa from bladder to blood. It is concluded that there is little or no difference in the *relative* migration rates of sodium and chloride ions across the mucosa of the ileum into the blood.

The chemical analyses of the fluid before and after its retention in the enlarged bladder are shown in Table IV. They are not of much value for our present purpose because it is

TABLE IV.—THE COMPOSITION OF AN ARTIFICIAL URINE BEFORE AND AFTER RETENTION IN A BLADDER WITH ADDED ILEAL LOOP TO WHICH ONE URETER IS ATTACHED

		Before retention	After retention
Time	min.	0	70
Volume	ml.	250	320
Cl	mEq.	16	26·8
Na	mEq.	15·2	24·0
K	mEq.	5·76	7·38
Urea	mg.	3·25	2·72

impossible to make accurate comparisons between the fluid before and after its retention in this modified bladder because of the urine entering the bladder from the transplanted ureter.

Ileo-cystoplasty.—The second patient was a woman aged 61 with a contracted bladder, the capacity of which was only 60 to 80 ml. A loop of lower ileum of length 23 cm. was anastomosed laterally to the top of the bladder, the capacity of which was thereby increased to about 260 ml. A similar investigation to that already described was then carried out in which Na^{24} and Cl^{38} were introduced into the enlarged bladder as part of an artificial urine (Table V). This urine was retained for an hour during which time blood samples were taken at suitable intervals and their radioactivities measured and analysed. Fig. 6

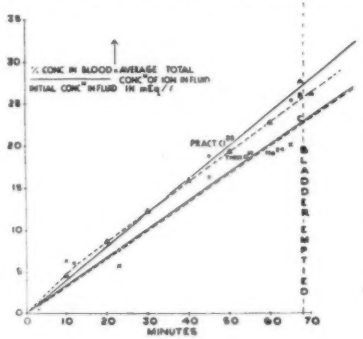

FIG. 6.—The absorption of Na^{24} and Cl^{38} ions from a bladder enlarged by the addition of an ileal loop, and the subsequent uptakes of these ions by the blood. AB represents the true differential uptake after 70 minutes of Cl^{38} ions relative to that of Na^{24}, expressed in mEq./l.

TABLE V.—A. N., FEMALE. THE COMPOSITION OF THE ARTIFICIAL URINE USED

	Grams/litre
Sodium chloride	15·2
Urea	14·0
Sulphuric acid	2·45
Ammonium bicarbonate	1·94
Potassium dihydrogen orthophosphate monohydrate	3·49
Creatinine	1·00
Hydrated magnesium sulphate ..	1·50
Calcium lactate	1·11

shows the results obtained. Once again the difference AB between the experimental and theoretical uptakes of chloride ions relative to that of sodium ions is very small, thus indicating that sodium and chloride ions are absorbed by the blood from the ileum in approximately equivalent proportions. This conclusion is supported by the comparison between the fractional losses of Cl^{38} and Na^{24} ions from the enlarged bladder (Table VI).

TABLE VI.—COMPARISON BETWEEN THE FRACTIONAL LOSS OF Cl^{38} AND Na^{24} IONS FROM A BLADDER ENLARGED BY A LOOP OF ILEUM. THE LOSSES ARE CORRECTED FOR ISOTOPIC DILUTION (A. N. ♀)

$$\frac{\text{Fall in concn. of } Cl^{38} \text{ ions}}{\text{Initial concn. of } Cl^{38} \text{ ions}} \times \text{Av. concn. of } Cl^{-} \text{ ions in bladder fluid in mEq./l.} = 51 \text{ mEq./l.}$$

$$\frac{\text{Fall in concn. of } Na^{24} \text{ ions}}{\text{Initial concn. of } Na^{24} \text{ ions}} \times \text{Av. concn. of } Na^{+} \text{ ions in bladder fluid in mEq./l.} = 50 \text{ mEq./l.}$$

In this case it was possible to show that absorption of potassium results from the contact of a fluid containing 28 mEq./l. of potassium with the ileal mucosa for one hour. Such a

potassium concentration approaches that likely to be found in urine. The significance of this finding will be discussed in the next case where it was possible to study this point more fully.

The perfusion of an isolated loop of ileum as an auxiliary kidney.—As a form of palliative treatment of a woman suffering from congenital cystic kidneys, a loop of terminal ileum 120 cm. in length was isolated and the two ends of the loop brought to the surface of the body in each iliac fossa (Fig. 7). Continuity of the small intestine was restored by lateral

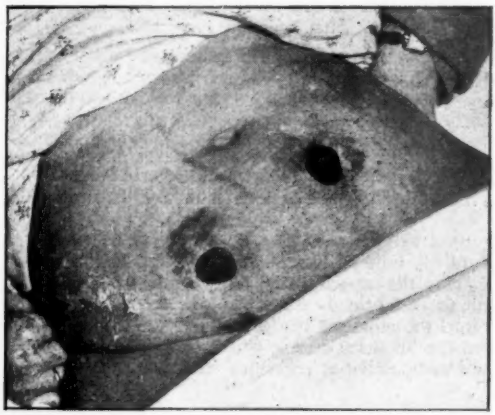

FIG. 7.—The use of an isolated loop of ileum as an auxiliary kidney. The two ends of the loop can be seen in the iliac fossæ.

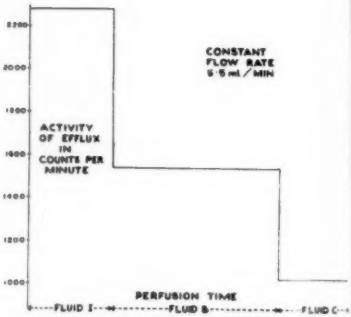

FIG. 8.—The relationship between the radioactivity of the efflux and the potassium concentration of the perfusion fluid used.

anastomosis. This isolated loop was perfused with a suitable fluid in order to promote the transfer of certain ions, urea and perhaps toxic material between the blood and this fluid. That some toxic material was washed out is probable in view of the fact that clinical improvement occurred after almost every perfusion. During the perfusion, particular attention was paid to the movement of potassium ions. Throughout each period of perfusion, the patient was kept on an approximately constant diet, low in both protein and salt. It was thought possible that the absorption or excretion of potassium depended upon the concentration of potassium in the perfusion fluid relative to its concentration in the plasma. In order to investigate this hypothesis, a series of perfusion fluids of different concentrations was made (Table VII), based on a fluid used by Kolff (1947). These were used one by one at a steady

TABLE VII.—THE COMPOSITION OF FLUIDS USED TO PERFUSE THE ARTIFICIAL KIDNEY

Isotonic		Hypertonic A	Hypertonic B	Hypertonic C
Sodium chloride	6·0 g./l.	The	The	The
„ bicarbonate	2·0 „	isotonic	isotonic	isotonic
Potassium chloride	0·4 „	solution	solution	solution
Glucose monohydrate	15·0 „	plus 0·4 g./l.	plus 0·8 g./l.	plus 1·2 g./l.
Calcium lactate	0·77 „	of	of	of
Hydrated magnesium sulphate	0·31 „	potassium	potassium	potassium
10% CO_2 90% O_2 to saturation		chloride	chloride	chloride
Total no. of mEq./l.	340·0	350·8	361·6	372·4

flow rate and a number of samples of the efflux were analysed for potassium. It was found that there was an excretion of potassium into the loop when an isotonic perfusion fluid was employed but when the original potassium concentration in the perfusion fluid exceeded the relevant plasma potassium concentration by a factor of from two to three, *reversal* of *net* potassium movement took place and with it a net absorption of potassium from the gut. This latter finding confirmed the result obtained in the second case of ileo-cystoplasty just described and suggests that a net absorption of potassium would occur if urine were allowed to flow through a length of ileum. In both patients concerned, the red blood cell potassium levels were normal.

In order to confirm this finding, radioactive potassium, K^{42}, was administered intravenously and the radioactivity of the perfusion efflux was measured in a special flow type

of Geiger counter. It was found that as the potassium concentration of the perfusion fluid increased, the radioactivity of the efflux decreased (Fig. 8), i.e. less potassium moved from blood to perfusion fluid as the potassium concentration of the perfusion fluid increased. However, even when chemical analysis of the perfusion efflux showed a net absorption of potassium from the gut, the efflux still showed radioactivity, thus demonstrating quite clearly the dynamic nature of the equilibrium governing potassium migration.

Table VIII shows the changes in blood potassium associated with the use of a series of

TABLE VIII.—CHANGES IN BLOOD POTASSIUM ASSOCIATED WITH THE PERFUSION OF AN ISOLATED ILEAL LOOP

Before perfusion Blood K mEq./l.		After perfusion Blood K mEq./l.		Types of fluid used	Time of perfusion in days
Cellular	Plasma	Cellular	Plasma		
86	6·15	83	6·0	Isotonic—then hypertonic A	2½
—	5·5	—	4·7	Isotonic—then hypertonic B	2½
78·2	5·26	88·5	4·62	Hypertonic B	3
74·4	3·98	87·1	4·81	Hypertonic B	3

perfusion fluids. It can be seen that the changes in blood potassium values reflect those changes in the potassium composition of the perfusion fluids already observed by chemical analysis of these fluids before and after passage through the loop of ileum.

It was found that for values of the sodium chloride concentration in the perfusion fluid of about 125 mEq./l. there appeared to be no significant net uptake of either sodium or chloride ions and therefore no significant difference between the net uptakes of either. This sodium chloride concentration approximates to that found in normal urine.

Net absorption of sodium chloride from the gut seems to be favoured by a high sodium chloride concentration in the ileal fluid; this may corroborate the greater absorption of Na^{24} and Cl^{38} ions from the gut noticed in the case of the enlarged bladder (Fig. 6), when the sodium chloride concentration in the gut was about 260 mEq./l., compared to the case of the uretero-ileocystoplasty (Fig. 5) when the sodium chloride concentration in the gut was only 60 mEq./l.

Summary.—(1) The migration of sodium, chloride and potassium ions across the bladder mucosa and also across the mucosa of the ileum is a dynamic process in which movement in both directions takes place simultaneously.

(2) In the case of a fluid in contact with the mucous membrane of the ileum and having a sodium chloride content similar to that found in urine, there appears to be only a small, unimportant net uptake of sodium chloride via the ileal wall. However, for sodium chloride contents approaching the physiological maximum for urine, a marked net absorption of sodium chloride from the ileum is observed. It was found that absorption of sodium and chloride ions took place to almost the same extent, so that it is unlikely that a hyperchloræmic acidosis will arise from a differential uptake of chloride over sodium ions across the mucosa of a loop of ileum attached to the bladder.

(3) When the potassium concentration of fluid in contact with the mucosa of the ileum is less than two to three times that of the relevant blood plasma, a net excretion of potassium from blood to ileum takes place. But when the potassium concentration of fluid in contact with the mucosa of the ileum is almost three times that of plasma, and the cellular potassium is normal, the direction of net potassium movement is reversed and there is a net absorption of potassium from the ileum. Thus, if urostasis should occur in a patient with an ileal bladder, there may be a real danger of hyperkalæmia.

The author wishes to thank Mr. L. N. Pyrah for permission to use his cases and Mr. G. W. Reed and Professor F. W. Spiers of the Department of Medical Physics, University of Leeds, for their whole-hearted co-operation in this work. He would also like to record his appreciation of the technical and secretarial assistance provided him by the staffs of the Department of Urology, University of Leeds, and the Department of Medical Photography, St. James's Hospital, Leeds.

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The Prevention and Control of Decubitus Stone Formation

By M. F. NICHOLLS, M.Chir., F.R.C.S.

St. George's Hospital and Royal National Orthopædic Hospital, London

DURING twenty-three years' association with a long-stay orthopædic hospital remarkably few cases of calculus have been treated surgically. This is not due to chance, nor a true sample of the usual frequency of calculus formation in patients immobilized for skeletal or other disease, but because the Royal National Orthopædic Hospital has always had this complication in mind and steps have been taken to prevent it from the outset.

The series we produce consists of all such cases that have come under our notice since 1945. In several instances their early treatment had been elsewhere and the stones were already present when they came under our care.

TABLE I.—26 PATIENTS WITH DECUBITUS STONES OR SLUDGE AT R.N.O.H. 1945–1955

Pott's paraplegia	6	Tuberculosis hip or spine ..	14
Traumatic paraplegia	2	Anterior poliomyelitis ..	4

It is in the nature of tuberculous disease of bones and joints and of its treatment that decalcification is severe and that the dangerous results of calculus formation are most often seen when the original lesion is cured or well under control. It is a tragedy—and it should be an avoidable one—that death from this complication should nullify years of patient and successful orthopædic treatment. In our series we have 2 such deaths. There are also 2 deaths due to decubitus calculi complicating anterior poliomyelitis. Paralytic ileus is a frequent complication of the severe and of the fatal cases.

The stones vary in composition, consistency and opacity to X-rays. All have calcium—the most common composition is calcium phosphate—but triple phosphates, calcium oxalate and mixtures of all these have occurred. The chemistry does not seem to be significant in prevention or treatment.

Our experience of solvents such as solution G has not been a happy or successful one and we believe that the cure of the condition is either by passage through natural channels or by operative removal if this fails.

TABLE II.—28 SEQUELÆ TO RENAL LITHIASIS IN 26 PATIENTS

Stones passed	10	Stones removed	14
Sludge passed	3	Stones found at post-mortem	1

In 2 patients stones were passed from one kidney and removed from the other.

In some instances only one kidney was affected.

Indications for operation.—If possible operative interference should be delayed until the patient is ambulatory. When orthopædic colleagues ask the advisability of such operations as joint fixation, the answer depends on the degree of impairment of renal function and the presence of renal infection. If these are not menacing it is better to postpone kidney surgery until the bone and joint lesion is stabilized—or until the patient can walk or at least be mobile and upright in a chair. Occasionally, however, delay is dangerous, as when infection is uncontrollable or when a stone plugs the kidney or ureter.

Nephrolithotomy, especially in the presence of spinal lesions, may be of extreme technical difficulty and the approach to the kidney may have to be unorthodox.

In any event excision of the 12th, and sometimes the 11th rib as well, is necessary if the kidney is to be mobilized without undue trauma. Where stone formation pervades the whole pelvi-calyceal system, complete removal is often very difficult and may be impossible without splitting the kidney through its cortex. The last manœuvre may be followed by troublesome post-operative hæmorrhage, but this has not been uncontrollable. Nephrostomy may be used for a time after the operation. This is a safeguard, as the ureter may become blocked with clot or debris, but it has the disadvantage that after a time infection along the track is extremely difficult or impossible to avoid.

As already indicated no benefit has resulted from lavage with acidifying solutions through such a nephrostomy.

In the aftercare it is essential to achieve complete control of infection by the appropriate antibiotics. This is usually impossible before the removal of the stones.

With modern methods of treatment of bone and joint tuberculosis, i.e. antibiotics and early fixation, the problem should arise much less frequently. The patients are mobilized earlier and it is hoped general and even local skeletal osteoporosis will be lessened.

Once established, calculus formation is difficult to manage and may indeed be uncontrollable and fatal.

The Prevention and Control of Decubitus Stone Formation

By F. Harwood Stevenson, M.D., M.R.C.P.

Royal National Orthopædic Hospital, London

The problem of decubitus stone formation results from the fact that immobilization produces metabolic changes which include a negative balance for calcium phosphorus and nitrogen (Beattie, 1947; Cuthbertson, 1929; Dietrick *et al.*, 1948; Whedon, 1951). Patients who are normally in balance or in positive balance for calcium with a urinary calcium output of 100/150 mg. daily on a normal diet, may, when immobilized, lose as much as 300/500 mg. calcium *per diem* in the urine. Indeed the osteoporosis so induced may even cause a rise of serum calcium to between 11 and 12 mg.%. There is a steady loss of bone trabeculation as a result of an imbalance between the activity of the osteoclasts and osteoblasts.

At the Royal National Orthopædic Hospital, Stanmore, where we have to give special consideration to this problem, attempts to prevent immobilization osteoporosis and its secondary effects, including stone formation, have been made. Steroids have been shown in animals and man to be capable of lessening the loss of bone from the skeleton (Gillespie, 1954; Reifenstein and Albright, 1947). We have not, however, felt justified in interfering with sex hormone metabolism in children and young adults in view of the possible secondary physical and even psychological effects. An increase of calcium in the diet acts temporarily upon the negative calcium balance, but after a short time merely produces an increased urinary calcium output. Raising the vitamin D intake, short of potentially toxic doses, has no effect. Even in doses over 50,000 units daily it increases absorption and lowers the fæcal calcium but the extra calcium is not retained but merely reappears in the urine.

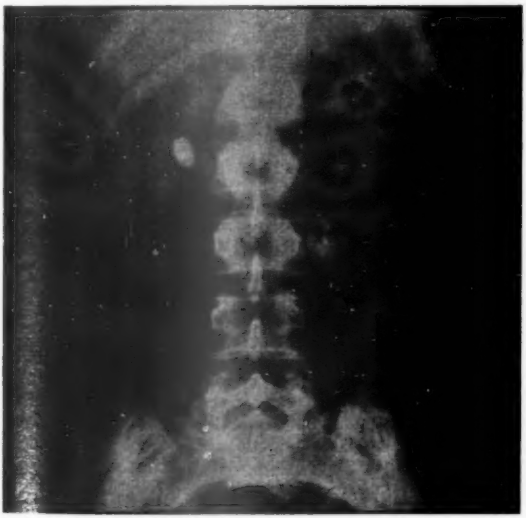

Fig. 1.—Renal stones in a patient with severe paralytic poliomyelitis. That on the right side suddenly blocked the renal pelvis and had to be removed.

We hoped that the use of plaster beds for our immobilized patients, supported on compound pulleys so that the position of the patient in space could be frequently changed, might have some effect upon the calcium balance. The results of experiments in the Metabolic Unit at the Royal National Orthopædic Hospital, however, were disappointing, as there is no effect upon the calcium balance. We have found, of course, that for some of our tuberculosis patients the period of conservative treatment is shorter since the use of chemotherapy (Stevenson, 1954). But, by and large we have to accept the risk of stone formation, and guard against it in the following ways.

Fluid intake is kept high. The compound pulley suspended bed is used merely as a means of changing position (Dommisse and Nangle, 1947). In some cases it may be valuable to lower the phosphate-containing articles of diet or even to divert phosphate into the fæces by precipitation with aluminium salts. Aluminium hydroxide or basic aluminium carbonate gel may be used (Shorr and Carter, 1950; Freeman and Freeman, 1941; Shorr, 1945). The absorption of phosphate is thus diminished and a urinary output of phosphorus of perhaps 800–1,000 mg. a day may be reduced to 200 mg. This method is particularly valuable where stones have been present, and the patient has chronic infection of the urinary tract with urea-splitting organisms with consequent impossibility of acidifying the urine.

Routine microscopy of the urine is essential at regular intervals. Macroscopic hæmaturia,

of course, is an immediate indication to check for stones, but so is microscopic hæmaturia, and on a number of occasions quite small amounts of blood such as 10/20 red cells per one-sixth inch field in the centrifuged deposit has given warning of the presence of small stones. This is particularly valuable, as increase in movement and fluid intake at this stage is usually successful in washing out the stones without surgical intervention. On other occasions sudden severe pain has drawn our attention to the existence of stone. Fig. 1 shows the renal tract area of a patient who had been severely paralysed by anterior poliomyelitis a year before. She had turned over on a couch during physiotherapy, and been seized with sudden pain in the right loin. Radiology disclosed several stones in the right ureter and one blocking the pelvi-ureteric junction. Surgery of course was, in this case, necessary. The importance and value of a good liaison with a urological surgeon cannot be too much stressed. The necessity may be mentioned in particular for surgical intervention, especially in the presence of bilateral stones, if there is anything to suggest the possibility of even partial obstruction. The patient should not be allowed to reach the stage of a rising blood urea before operation.

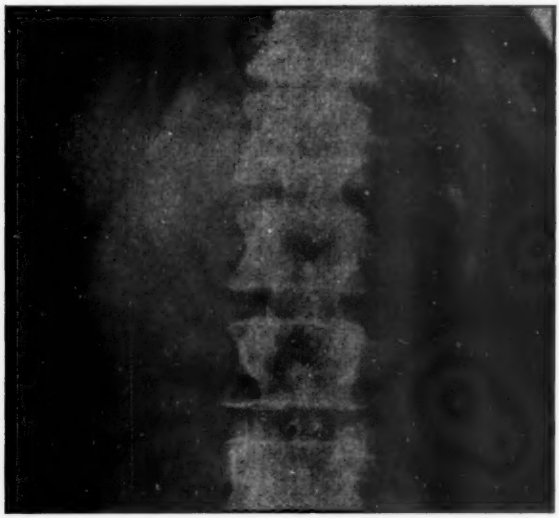

FIG. 2.—Mineral sludge in the calyces of both kidneys in a patient immobilized for tuberculosis of the spine. Movement in a compound pulley suspended plaster bed and high fluid intake removed it before true stone formation had occurred.

In some patients it has been possible to remove quite large masses of mineral deposits by partial mobilization and increased fluid consumption where there was reason to believe that the deposits were not true stones but masses of mineral sludge. Fig. 2 is an X-ray of such a patient with deposits in the calyces of both kidneys. A film taken in another hospital six weeks before admission had shown his renal areas to be clear. Treatment succeeded in ridding him of the deposits in his kidneys in a few weeks and they did not return.

In summary then, it may be stated that the danger of stone formation, particularly in orthopædic tuberculosis, severe anterior poliomyelitis and after spinal injuries, must always be remembered. High fluid intake, and as much movement as possible, combined with constant vigilance for symptoms or urinary evidence of stone formation will frequently enable the trouble to be discovered and remedied before the stage of inevitable surgery.

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BOOK REVIEWS

Modern Trends in Blood Diseases. Edited by John F. Wilkinson, M.D., M.Sc., Ph.D., F.R.C.P., F.R.I.C. (Pp. viii + 359; 91 black and white illustrations, 2 colour plates. 65s.) London: Butterworth & Co. (Publishers) Ltd. 1955.

This book aims at being a guide to the present trends of the more important clinical and experimental aspects of hæmatology during the last twenty years. With such a laudable aim it is disappointing to find some important subjects neglected and several included which come doubtfully within the book's alleged scope.

Amongst the most serious omissions is any consideration of polycythæmia, its relation to other myeloproliferative disorders, and its treatment which has progressed so successfully in the last decade. In addition there is no mention of the thrombocytopenias and disorders of coagulation. Nothing significant is written either about myelomatosis which, with its protean manifestations and biochemical interest, merits inclusion somewhere. On the other hand, subjects whose inclusion seems of doubtful value are those on the fundal changes and bone changes of blood diseases.

The chapter on hæmatological techniques is orthodox but unfortunately stresses red cell counting without considering its statistical assessment, and no mention is made of the value of the hæmatocrit and the importance of centrifugal force and its duration in refining its accuracy. This chapter also omits to mention the value of serial section of bone-marrow aspirates.

A few chapters set a high and rewarding standard in this book. Finest of these is an excellent and lucid discussion of iron metabolism by two people who have played such a notable part in its research, Drs. Moore and Dubach. This chapter makes excellent reading and, taken with the discussion by Drs. Cartwright and Wintrobe on the anæmia of infection, is the highlight of the book. Other good chapters include that on the blood pigments by Dr. Rimington and those on anticoagulant therapy and iso-immunization.

Two chapters on leukæmia leave the impression that they could be condensed, and some of the tables assessing treatment by different antimetabolites include so few patients that they would be better omitted. The hæmolytic anæmias are discussed by Drs. Crosby and Damashek, but here, after a promising start, the authors attempt to cover too much ground and there is room for little more than a brief comment about most of the subjects.

Other subjects covered include the dermatological aspects of blood diseases, pædiatric hæmatology, vitamin B_{12} and the reticuloses. On the whole much of this book proves disappointing both from the point of view of the ground covered and the individual merit of some of its chapters; two or three of these are, however, of high quality.

Diagnosis and Treatment of the Acute Phase of Poliomyelitis and its Complications. Edited by Albert G. Bower, M.D. (Pp. x + 257; 64 figs. 50s.) London: Baillière, Tindall and Cox. 1954.

This is a good example of an American teamwork production. There are fourteen contributors who deal with the subject from the point of view of Diagnosis, General Management, both Medical and Nursing, with valuable contributions from an E.N.T. Surgeon, Radiologist (particularly having regard to chest complications), Orthopædist, and Obstetrician, as well as chapters upon the help to be obtained from Physical Medicine, and the biochemical changes which occur especially in respiratory failure. There is, also, a contribution on the subject of transfer of acute cases, and a chapter upon mechanical apparatus. It would be a pity if such detailed work gave the impression, to those who see respiratory poliomyelitis infrequently, that it was impossible to save life without attention to all the points discussed. It is true also that, with the best apparatus and team of experts for the handling of an epidemic, much depends upon experience as well as upon detailed thought and care, particularly when there is a high proportion of bulbar cases. It has elsewhere been found that the death-rate is high in the beginning of an epidemic, and tends to become lower as the epidemic proceeds, simply because of this gain in experience. Although one

hopes that in this country we may not be faced with a large and serious epidemic, we never know when one may occur. In consequence one welcomes a book of this sort, produced as it is by a team who, in the last seven years, have had 11,000 patients through their unit.

The chapter on General Diagnosis follows normal lines. The author on Medical Management of the patient covers a wide field, and indeed overlaps other chapters. We are not by any means all of us yet accustomed to the thought that the blood biochemistry of a patient with respiratory insufficiency who is having to be sedated and fed artificially must inevitably be considered in considerable detail. Tracheotomy and its indications and the subsequent care of the patient figures prominently in a number of the chapters. In all there is a clear basis of principle laid down before discussion of detailed applications. This is particularly valuable in the diagnosis and care of respiratory failure, and in electrolyte and other biochemical changes. There is also a useful discussion upon "weaning" from the respirator. The final chapter gives an account of the actual experience of a County Emergency Team for the treatment of acute poliomyelitis with respiratory failure.

High Blood Pressure. By George White Pickering, M.A., M.B., M.D., F.R.C.P. (Pp. viii +547; 106 illustrations, 5 in colour. 65s.) London: J. & A. Churchill Ltd. 1955.

Pickering has contributed several papers to the medical literature on the subject of systemic hypertension since 1934, and his authorship now of a book embodying his own views, and those of others, on High Blood Pressure is both natural and welcomed.

It is on the subject of so-called Essential Hypertension that Pickering expresses newer views. He rejects the older concept that such patients differ qualitatively from those with normal pressure and that a sharp distinguishing line can be drawn between the two. In the same way he opposes the division into the three clinical stages of prehypertension, labile hypertension, and fixed hypertension. Instead, he offers three propositions. The first concerns the nature and pathogenesis of essential hypertension. Arterial pressure, like height, weight and other measurable characteristics, shows a curve of continuous variation in the population at large. Unlike height, the distribution curves are very different at different ages after adolescence is finished, and the average values for arterial pressure tend to rise steeply in the older ages. It seems that essential hypertension represents little, and perhaps nothing, more than the upper end of the distribution curve, designated as essential hypertension at some arbitrary level such as 150 systolic, 100 diastolic. The difference between subjects with essential hypertension and those with lower pressures is quantitative and not qualitative, a matter of degree and not of kind. It is suggested that essential hypertension is the resultant of the interaction of the genetic and environmental factors that operate in the population at large. Of these, the influence of age and inheritance can be defined approximately. The author's second proposition is that when arterial pressure is raised long enough by some specific interference, the arterial pressure may remain relatively high when the original interference is removed. This proposition may be of great importance particularly in relation to the possible role of environmental factors in essential hypertension. The third proposition is that the malignant phase of hypertension is a consequence of the degree to which arterial pressure is elevated and the speed with which that elevation is attained. The malignant and benign phases of hypertension thus express differences in degree and not in kind. The occurrence of the malignant phase probably partly accounts for the observed fact that there is a ceiling above which arterial pressure does not rise. The importance of this hypothesis to therapeutics needs no emphasis.

Although he uses the term hypertension throughout the book, the author dislikes it on the grounds that adoption of the term in the past has led to the practice of distinguishing between normal blood pressure and hypertension and so to the assumption that those subjects with hypertension necessarily differ from the rest of mankind.

Under coarctation hypertension the author collects evidence from the work of other writers to show that although surgical treatment reduces the arterial pressure, it leaves it at a higher level than in the normal. Pickering cites this as another instance where removal of the abnormality, originally responsible for the hypertension, fails to restore the blood pressure to the expected normal value.

When dealing with nephritic hypertension, perhaps too much space has been devoted to nephritis itself, and similarly the treatment of hypertension is dealt with too elaborately and without the author's commendation or condemnation of particular remedies. Chapter 24, however, enumerating practical hints concerning the diagnosis and management of patients with high blood pressure, is exemplary.

The book is clearly written, well illustrated, and deals comprehensively with the difficult clinical state where the blood pressure is raised to an unusual level. No research worker on the subject, teacher of either undergraduate or postgraduate students, or for that matter the student himself, should be without this very useful book.

Reflections on Renal Function. By James R. Robinson, M.D., Ph.D. (Pp. 163; 3 illustrations. 17s. 6d.) Oxford: Blackwell Scientific Publications. 1954.

This little book sets out resolutely and concisely the modern views on kidney function. It is particularly suited to those who are not in the renal field but who wish to bring themselves up to date with the vast literature which has grown up around the kidney. Its title suggests a serious consideration and perhaps evaluation of the controversial aspects of kidney function, but instead it gives the conventional theories in dogmatic form, which perhaps would not always suit those of a more enquiring mind, and indeed there would be some in the renal field who would not care to express their feelings so whole-heartedly. Nevertheless, Doctor Robinson approaches the problem from a physiological standpoint. He is obviously a first-class teacher, writes concisely and clearly and from this point this book will be useful as a rider to Homer Smith's authoritative volume on the same subject.

The Visual Fields. By Brodie Hughes, M.B., B.S., Ch.M., F.R.C.S. (Pp. ix + 174; illustrated. 35s.) Oxford: Blackwell Scientific Publications. 1954.

"This book", writes the author, "is a statement of one man's views and experience of a particular subject" and since he is a neurosurgeon the emphasis is on injuries, vascular disease and compression lesions, whereas ophthalmic and medical conditions receive less attention. This circumstance in no way reduces the value which this authoritative monograph will have for the ophthalmologist and the neurologist who are so often the first to see the case which is destined to become a surgical problem.

Professor Hughes provides an up-to-date account of the applied anatomy of the visual pathways, and of their vascular supply, and the text gives substance to his claim that careful study of the visual fields can help the clinician to "hazard a guess as to the pathology as well as to estimate its anatomical location". The correlation between a particular type of field defect and a specific injury or disease has, of course, been known for many years but the extent of this correlation and its usefulness in diagnosis is not always realized. To be of value, studies of the visual fields must be carefully carried out and accurately recorded. This is a time-consuming task which cannot be delegated to an inexperienced technician and this no doubt has played a part in preventing the technique from being more widely used. Yet it is to be doubted whether the time spent on the examination of the fields is any greater, or any less rewarding, than what is customarily and uncomplainingly devoted to some other methods of investigation.

It is refreshing to read that Professor Hughes uses the simple methods of perimetry and scotometry as advocated by the late Dr. Traquair, and that he avoids gadgets and complicated machinery.

In general the proof reading has been good but in Fig. 142 the visual field charts appear to have been muddled up—b) should be a), c) should be b), d) should be c), and a) should be d).

In Fig. 27 it should have been stated that the diagrams refer to the left side. The statement on Page 152 that "in most cases of retro-bulbar neuritis which are left with a permanent field defect, this is due to secondary optic atrophy rather than persistent scotoma" leaves one in doubt as to what the author really means.

There are several statements made in this book which are not quite in line with modern views, e.g. (1) Page 70 "There is some anastomosis between the central (retinal) artery and the choroidal circulation at the periphery of the retina". It would appear, however, that Bruch's membrane, in its healthy state, forms an impenetrable barrier to the passage of blood vessels (Michaelson, I. C., in "XVI Concilium ophthalmologicum 1950, Britannia", 1, 611) so that a chorio-retinal vascular anastomosis in that situation is not possible. (2) Page 163 "The initial field loss in Glaucoma is an arcuate scotoma". Although this may often be true in the case of chronic non-congestive glaucoma, it is by no means true of other varieties of that condition.

The book provides an excellent chapter on a technique of perimetry and the method of recording results. It should do much to popularize this method of examination and its appeal is enhanced by the excellence of production and profusion of illustrations. The text is clear, in the main, but undue condensation brings obscurity to certain passages, a fault which can be corrected in the later editions which this book will surely achieve.

A Symposium on Adrenal Function in Infants and Children, November 3 and 4, 1954, Department of Pediatrics, College of Medicine in Syracuse. Edited by Lytt I. Gardner, M.D. (Pp. 112.) Syracuse, N.Y.: State University of New York. 1954.

This little booklet is a collection of abstracts of papers given at the College of Medicine in Syracuse. There are twenty-one contributions covering a wide range of the subject, and, being in abstract form, are delightfully brief. Joan G. Hampson discusses the psychological status of children with hyperadrenocorticism, and wisely concludes that even from childhood a change from assigned sex is undesirable unless possibly specially requested by the individual. Rosenthal and Bronstein report favourably on the use of desoxycorticosterone trimethyl-

acetate in the adrenal insufficiency of adrenal cortical hyperplasia. A strange and most interesting case of adrenal and hypoparathyroid insufficiency is discussed by Forbes of Rochester. At first sight this appears a great rarity but is nevertheless another authentic instance of multiple endocrine lesions in the same patient. Edna Sobel gave valuable consideration to the effects of testosterone and cortisone on skeletal growth and maturation. Children of 5–10 years were surprisingly sensitive, as far as growth was concerned, to 5 mg. methyl testosterone daily, but skeletal maturation tended to outpace skeletal growth. The exact outcome of cortisone treatment on growth in children with adrenal hyperplasia seems to need further study, as delay of maturation appears to be accompanied by delay of growth as one would expect. The remaining papers are of more biochemical or clinical pathological interest dealing with steroid metabolism.There is a brief but important review on aldosterone by Gaunt and Renzi and space is given to Dorfman's views on the ætiology of the adrenogenital syndrome. There are two contributions on maternal steroid levels. Valuable data on salivary electrolytes in infants are given by Prader and his colleagues and related to the probable state of adrenal function in these children.

In summary this book is of great value to the specialist as the abstract method of presentation assumes considerable knowledge. It is produced in handy form. An innovation is the summary at the end of each paper in "Interlingua" which would appear to be of great value to South American readers. These summaries suffer from the disadvantage of all foreign language summaries that they tend to be too short to be of much practical value.

The Health of the Elderly at Home. By William Hobson, B.Sc., M.D., D.P.H., and John Pemberton, M.D., M.R.C.P. (Pp. xvi + 238; illustrated. 30s.) London: Butterworth & Co. (Publishers) Ltd. 1955.

All physicians interested in general medicine and alive to the problems of old people in the community to-day should read this new publication.

In giving their report it is obvious that the authors have undertaken their survey with great care and precision and their detailed and critical records of elderly patients living at home in the area of Sheffield is therefore of great value at this time. Although the numbers in many instances are too small to allow of dogmatism, the fact that so many of the findings so nearly approximate to those found in the Wolverhampton survey carried out by Sheldon in 1947 adds considerable interest and importance to the present work.

The extent and limitations of their investigations are well documented and the aims of the survey are accurately noted. For these reasons the book can well be used for reference. The sections relating to different systems are all factual and well arranged and the sections on cardiovascular disease and on hypertension will prove of great interest to all clinicians. The study of conditions as common as vertigo, tinnitus, angina of effort, clinical arteriosclerosis, &c., in relation to hypertension are excellent in their simplicity and brevity. Such data must promote a more accurate assay of these conditions when encountered in the general medical investigation of patients. The chapter on nervous conditions with reference to mental states and brief clinical histories illustrating psychiatric conditions adds a subject too often ignored.

The authors are to be congratulated on their introduction of the subject of blood chemistry and their findings should provoke numerically larger studies into some of these fascinating conditions.

The survey includes a study of dietary and this is related not only to sex, age groups and types of food, but also to calorie values and to social conditions. These latter aspects are essential to a full appreciation of nutrition in the older age groups when treated in their own homes.

The introduction of the subject of work and its effect upon the physical and mental well-being of older persons is also appropriate.

In the last section entitled "Conclusions" the authors have summarized their findings most conveniently and have introduced some new ideas on research for the future which are worthy of attention.

The handbook is brief and presents a good piece of work critically undertaken and precisely recorded and is highly recommended.

The Medical Significance of Anxiety. By Richard L. Jenkins, M.D. (Pp. 46. $1.00.) Washington: The Biological Sciences Foundation, Ltd. 1955.

This is an excellent little monograph on Anxiety dealing in three sections with its importance, its control in medical practice, and its nature. It reveals little that will be new to psychiatrists, but it is not written for them. It should be helpful to the general physician and general practitioner who are interested in the phenomenon of tension, but at a loss to know how to deal with it. It follows with sureness a middle course between reconditeness and naïveté.

Section of Pædiatrics

President—G. H. MACNAB, M.B., F.R.C.S.

[*February* 25, 1955]

MEETING AT THE VICTORIA HOSPITAL FOR CHILDREN, TITE STREET, CHELSEA

Virus Pneumonia with Increased Cold Agglutinins [*Abridged*]

By D. H. GARROW, B.M., M.R.C.P.

DURING the 1930s reports began to appear in America of a form of pneumonia which was considered to be unusual. Many different synonyms were used to describe it until, in 1942, the Surgeon-General of the U.S. Army proposed the term "primary atypical pneumonia (ætiology unknown)". Although a case of pneumonia with increased cold agglutinins had been described in 1918 by Clough and Richter, it was not until 1943 that the frequent association of increased cold agglutinins with primary atypical pneumonia was described independently by Peterson, Ham and Finland in America, Turner in this country and Shone and Passmore in the Middle East. In 1944 the Commission on Acute Respiratory Disease carried out a well-controlled experiment in which pneumonia with increased cold agglutinins was successfully transmitted to human volunteers. Good evidence was provided that a virus was the cause. It also appeared likely that the same virus might produce a minor respiratory infection without increased cold agglutinins. There are two main reasons for the subsequent blurring of this clear picture. Firstly, cold agglutinins are present in low titre in the majority of normal people, and there has been disagreement as to what constitutes a significant increase. Secondly, virus pneumonia with increased cold agglutinins has frequently been confused with "aspiration pneumonia", a non-specific condition which often follows an upper respiratory infection.

Until recently virus pneumonia has been relatively uncommon, but during the past few months at this hospital there have been an unusually large number of cases: thus, of 40 cases diagnosed in the past year and a half, 18 occurred during November and December 1954. It is tempting to speculate upon the possible significance of this increase and suggest that there may recently have been an epidemic of virus pneumonia in London. In any case, it has served to make us familiar with a definite clinical entity.

Cases in which the diagnosis was not supported by laboratory findings have been excluded from the present series. Serological tests were carried out by Dr. J. A. Dudgeon. 39 cases were demonstrated to have cold agglutinin titres ranging from 1/40 to 1/1280. One child was not tested but is included because her mother and father subsequently developed pneumonia with increased cold agglutinins. In a large number of control sera the titre was in the region of 1/10 or less. A few children from whom blood was collected in the acute and convalescent phases were shown to have a rise in cold agglutinin titre of fourfold or greater, but in the majority of cases the first specimen was not taken until after the first week of the disease and no rise in antibody titre could be demonstrated. In only 11 cases was a streptococcus M.G. titre of 1/40 or greater demonstrated. Serological tests were also carried out for antibodies to influenza A, B and C viruses as well as psittacosis and Q fever. No significant titres were detected.

A clinical analysis of these 40 cases showed that in virus pneumonia (as opposed to aspiration pneumonia) upper respiratory tract symptoms before the onset of cough are rare. Although specifically enquired for they were absent in 32 cases. Cough was a troublesome symptom and in 9 instances suggested a diagnosis of whooping-cough. Retrosternal soreness or a "sore throat" localized to the suprasternal notch was common. Cyanosis which was out of proportion to the dyspnœa was well marked in 5 cases. Widespread physical signs suggesting bronchitis were common, being present at some stage in 27 cases. The X-ray appearances were very variable sometimes suggesting bronchiectasis, or more often, because of increased hilar root shadows, a primary tuberculous complex. A diffuse mottling was perhaps the most characteristic appearance and this occasionally resembled miliary tuberculosis. The picture was often, however, simply that of segmental collapse-consolidation. X-ray appearances remained abnormal as a rule for several weeks.

A study of the family contacts was made and it was found that 45 out of 113 persons at risk developed respiratory infections. In 28 of 31 instances in which the interval between the onsets was accurately known, it ranged from seven to twenty-three days, suggesting a long

incubation period. The nature of the infection was investigated in 22 cases: 14 were diagnosed as having pneumonia, 10 with increased cold agglutinins and 4 without. The remaining 8 cases were examples of a minor respiratory illness, of apparently long incubation period, but without increased cold agglutinins.

The above investigation was not planned to assess the relative value of different forms of treatment. 18 cases were, however, given no chemotherapy, 14 sulphonamides and/or penicillin and 8 Aureomycin. The impression was formed that not only were sulphonamides and penicillin ineffective but Aureomycin also in no way influenced the course of the disease.

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Commission on Acute Respiratory Diseases (1946) *Bull. Johns Hopk. Hosp.*, **97**, 109.
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TURNER, J. C. (1943) *Nature, Lond.*, **151**, 419.

DEMONSTRATION: **X-rays of Virus Pneumonia.**—Dr. K. JEFFERSON (for Dr. N. HAJDU).

FILM AND DEMONSTRATION: **Treatment of a Spastic Child.**—Dr. CLIVE SHIELDS.

FILM: **The Pump and Squirt Action of the Tongue in Sucking.**—Mr. E. GWYNNE EVANS.

The following cases were shown in rooms in the Out-patient Department:

? Christmas Disease.—Dr. L. ANDREWS (for Dr. CHARLES PINCKNEY and Dr. J. MARSHALL CHALMERS).

Sickle-cell Anæmia.—Dr. R. BARNES (for Dr. CHARLES PINCKNEY and Dr. J. MARSHALL CHALMERS).

Idiopathic Heinz-body Anæmia.—Dr. R. BARNES (for Dr. C. W. KESSON and Dr. J. MARSHALL CHALMERS).

Lymphatic Leukæmia in Remission Following ACTH.—Dr. L. ANDREWS (for Dr. CHARLES PINCKNEY and Dr. J. MARSHALL CHALMERS).

Congenital Hypoplastic Anæmia (Two Cases).—Dr. R. BARNES (for Dr. CHARLES PINCKNEY and Dr. J. MARSHALL CHALMERS).

Neutropenia of Unknown Ætiology.—Dr. S. WOLFF (for Dr. URSULA JAMES and Dr. J. MARSHALL CHALMERS).

Aplastic Anæmia after Chloromycetin.—Dr. R. BARNES (for Dr. URSULA JAMES and Dr. J. MARSHALL CHALMERS).

Idiopathic Hypercalcæmia in an Infant Treated with a Low Calcium Diet.—Dr. S. WOLFF with Mr. L. G. JONES (for Dr. URSULA JAMES).

Osteoid Osteoma.—Dr. D. H. GARROW (for Dr. C. W. KESSON).

(1) Unilateral Neonatal Gangrene of a Leg. (2) Von Recklinghausen's Disease, Tuberose Sclerosis, and Paget's Disease in the Same Family. (3) Pulmonary Histoplasmosis.—Dr. D. H. GARROW (for Dr. CHARLES PINCKNEY).

Nephrotic Syndrome Treated with ACTH (Three Cases).—Dr. CHARLES PINCKNEY and Dr. URSULA JAMES.

(1) Cystic Swelling in Submental Region. (2) Crohn's Disease in a Child of 2 Years.—Mr. RODNEY SMITH.

(1) Pulmonary Stenosis (Mild). (2) Atrial Septal Defect. (3) Ventricular Septal Defect. (4) Pulmonary Stenosis Plus Ventricular Septal Defect.—Dr. AUBREY LEATHAM.

Grice Operation for Paralytic Valgus Feet.—Mr. ROY H. MAUDSLEY (for Mr. CHARLES GRAY).

Congenital Anhidrotic Ectodermal Dysplasia.—Mr. A. NESBITT.

Two Gargoyles.—Dr. S. WOLFF (for Dr. CHARLES PINCKNEY).

(1) Hæmorrhage from a Meckel's Diverticulum. (2) Congenital Paroxysmal Tachycardia. (3) Congenital Lobar Emphysema. (4) Amaurotic Family Idiocy of Tay-Sachs. (5) Bilateral Retrolental Fibroplasia with Spastic Paraplegia.—Dr. C. W. KESSON.

[*March* 30, 1955]

DISCUSSION ON HYDROCEPHALUS OF INFANCY

Dr. **Hugh Jolly**: My interest in this subject dates from some three years ago when I was able to observe at first hand the work of Dr. E. B. Spitz, the neurosurgeon, in Philadelphia Children's Hospital.

No one doubts the depressing side of infantile hydrocephalus, but Wilder Penfield (1935) once commented that what the physician who continues to face this problem needs most is "fortified optimism" and it is in that spirit that the opening speakers are approaching the subject.

The incidence of hydrocephalus is approximately 0·2%, but all cases occurring during the first year of life may not have been included in this figure. Crenshaw and Banner (1952) wrote up a study at the Mayo Clinic over the years 1935–1949 where they found 24 hydrocephalic births out of 12,500 births, giving an incidence of 0·2%. Murphy (1937) analysed 935 malformed stillborn and liveborn infants who died in Philadelphia during a five-year period and found 273 cases of hydrocephalus, with or without spina bifida, out of a total of 130,000 cases. This also gives an incidence of 0·2%. Dr. Beryl Corner has very kindly given me recent figures from the Maternity and Southmead Hospitals, Bristol, and during the four years 1951–1954 there were 67 cases of live or stillborn hydrocephalus with or without spina bifida, out of 16,358 births, giving an incidence of 0·4%. The condition is somewhat commoner in boys than girls and, as Murphy has shown for all congenital malformations, the higher the age of the mother the greater the risk that she will produce a hydrocephalic child.

Clinical Features

The large head of the child with advanced hydrocephalus is obvious to everyone, but the early stages may not be so easy to detect in view of the variations in size of the normal head. At the same time, early treatment, and therefore early diagnosis, is essential if brain damage is to be prevented. The hydrocephalic head is globular, as opposed to the flat top of those children who happen to have a large head but have not got hydrocephalus—a condition which is sometimes familial and for this reason both parents should be seen. In this condition the facial features are usually proportionately large, whereas in the child with hydrocephalus they are relatively small and so are overshadowed by the globular top to the head. Healthy premature babies are sometimes mistaken for those with hydrocephalus because of the rapid growth of their heads, but this is a normal feature of their development.

It will be appreciated then that the actual size of the head is not pathognomonic of hydrocephalus. The size of the anterior fontanelle is also not diagnostic since many normal babies may have large fontanelles. However, the tension of the fontanelle is of the greatest importance since a rise in intraventricular pressure is the essential feature of the condition, and therefore all babies with hydrocephalus will have increased fontanelle tension except for those in whom the expansion of the skull bones has been sufficiently rapid to take up this increase of pressure. A rapid increase in head size does not necessarily indicate a tumour as the underlying cause of the hydrocephalus.

The child is usually remarkably placid and may take his feeds well although after operation we have found that feeds are usually taken very much more readily than before. Only as death approaches does the child become irritable and sometimes at this stage spasticity and even decerebrate rigidity supervene. It is of interest that Dandy (1940) found that spasticity came on earlier if there was obstruction at the foramina of Magendie and Luschka rather than at the aqueduct, and in fact the onset of spasticity is one of the strongest indications of a block at the basal foramina. Papilloedema is not a feature of infantile hydrocephalus and in Mr. Macnab's large series papilloedema has only been present if the hydrocephalus has been caused by a tumour.

The vital functions of the body are preserved to a remarkable extent even in the most advanced hydrocephalic, since the destruction of the brain involves the white rather than the grey matter and even the most severe case may have a normal thickness of grey matter. The intelligence will vary with the degree of loss of brain substance though there are some writers such as Putnam (1935) who believe that a large number of the hydrocephalic children with impairment of mentality have an associated congenital malformation of the cortex to account for their mental retardation.

Investigations

An X-ray of the skull is taken, particularly to exclude intracranial calcification as evidence of toxoplasmosis. The cerebrospinal fluid is examined, including its Wassermann reaction, although, as Professor Russell (1949) has shown, syphilis hardly enters into the ætiology

of hydrocephalus, contrary to past opinion. A rise in protein in the C.S.F. may be evidence of an intracranial tumour but could have resulted from earlier intraventricular bleeding, particularly during labour. Bilateral subdural taps are always made to exclude a subdural hæmatoma.

These examinations are followed by a dye test to determine the site of the obstruction. We have been using indigo carmine and 2 c.c. of this are injected into one ventricle and the other ventricle is tapped immediately afterwards to check the passage of the dye. Lumbar puncture is performed five minutes later and if no dye is present in the C.S.F. this is repeated after half an hour. If there is still no dye in the lumbar fluid we repeat the puncture in one hour and four hours, although only once has dye appeared in the later specimens when it was absent in the one taken at half an hour. When dye has failed to reach the lumbar fluid a cisternal puncture is performed to check if it has reached the cisterna magna. In some centres it is also the practice during this test to leave a catheter in the bladder to determine at what point dye appears in the urine. This may have some use in assessing the efficiency of the absorption mechanism but is of little value from the practical point of view of planning treatment.

Ventricular air studies should always be carried out in order to locate more accurately any block and to determine the likelihood of a tumour. 20–50 c.c. of air are injected into the ventricle after removal of an equal quantity of C.S.F. and this small quantity is just as efficient and much less dangerous, than the larger quantities which were used in the past. The head is positioned so that the shift of the air bubble allows a full radiographic examination of the ventricles and the X-rays should always include one taken in the upside-down position. These pictures will show the site of a block and also the thickness of the cortex. From all these investigations one can differentiate the communicating type of hydrocephalus, where there is free communication between the ventricles and the spinal subarachnoid space, from the obstructive type where no such communication exists. The differentiation of these two types is regarded by some workers as of dubious value but it is essential before carrying out the Spitz and some other types of operation which are only indicated for communicating hydrocephalus. The proportion of these two types is roughly equal—Sachs (1942) investigated 98 cases of hydrocephalus and found 54 to be communicating, 42 obstructive and two could not be classified.

Choice of Patient for Surgery

A decision must be made as to whether the child is suitable for surgery, and the first point to decide is whether the hydrocephalus is progressive, since obviously if arrest has already taken place no surgical treatment is indicated. If the answer to this question is not obvious a further period of observation is required.

In the past, children have been refused surgery for two principal reasons—a poor intellect or associated abnormalities, particularly spina bifida. It is very difficult to assess the future intelligence of any baby, and the only statement one can make with certainty is that if the thickness of the cerebral cortex—as measured on the ventriculogram and from the distance covered by the needle at ventricular puncture—is less than 1 cm. the child will be mentally defective. If the cortex is over 2 cm. the chances of a good intellect are reasonable whereas between 1 and 2 cm. no forecast can be given.

Most clinicians have seen patients with very large heads and a normal intellect and Putnam (1938) refers to a man who had a good intelligence despite a head circumference of 28 in. Head size is therefore of much less value than thickness of the cortex in the assessment of future intelligence. Penfield and Coburn (1938) record a case of a woman of normal intelligence who died at the age of 29 and was found to have an Arnold-Chiari malformation. An associated meningocele had been repaired when she was 3 years old. Scarff in 1942 showed that after an operation for hydrocephalus the cortex of a girl of 2 months became thicker. The author raises the question as to whether regeneration of the cortex may have taken place in this and other young infants where the hydrocephalus has been successfully relieved. Professor Russell feels that the answer lies in a reduction in the size of the ventricles. Doubtless, as a result, the cortex and particularly the subcortical white matter increase in depth through changes in the matrix of the cerebrum but this can hardly be called "regeneration".

The problem of picking cases for operation on the grounds of intellect would be much easier if those with a poor intellect were sure to die if left alone, in which case the operation would merely be causing a large number of mentally defective children to survive. In fact, however, many of these children if left alone do survive and this is a strong point in favour of operation on more of them in the hope that at least this may cause some improvement in their intellect even though one knows it cannot become normal.

The principal associated abnormality for which operation is refused is the menin-go-

myelocele but here again the same arguments hold. These children do not die with the rapidity that is commonly believed and if the meningomyelocele is removed they are much easier to manage and the area less painful. The common statement that operation on a meningomyelocele will precipitate the development of hydrocephalus is very doubtful. Approximately 50% of meningomyeloceles will be associated with hydrocephalus but the development of the hydrocephalus, where it is not present at birth, is almost certainly unrelated to any operation on the meningomyelocele.

Operation for communicating hydrocephalus.—Dr. Spitz of Philadelphia has now performed this operation on approximately 100 cases with a success rate of over 80%. The operation, a lumbar arachnoid-peritoneostomy, was first described by Ferguson in 1898, and Davidoff in 1929, reviewing the multitude of operations which had been tried, said that this basic method had produced the most promising results. Spitz has revived the operation with the aid of the new plastics and tubes now available. He also removes the omentum since this structure so often sealed off the peritoneal end of the drainage system.

The operation is performed with the child lying on his right side and two surgical teams work at the same time, one performing a laparotomy and the other a laminectomy over the lumbar 2nd–3rd interspace. The abdominal surgeon removes the omentum and this procedure must be bloodless in order to prevent any future adhesions. We have tried to remove the appendix as well, since obviously this is desirable, but it was not practicable in that position.

The surgeon performing the laminectomy passes a plastic tube into the spinal canal so that its tip lies alongside the cauda equina. The tubing is anchored to a spinous process and then passed anteriorly through the medial part of the erector spinæ muscles to come out just above the iliac crest and enter the peritoneal cavity. A special Teflon button made of lucite is attached to the peritoneal end of the tube which has a number of openings to allow of free drainage. After the operation it is usual for the anterior fontanelle to remain tense for twenty-four to forty-eight hours, but then it starts to become lax and eventually so sunken that its bony edges stand up like dry rocks at low water.

We have operated on only 4 cases because this is the number of suitable children with communicating hydrocephalus that we have had for treatment. In the first 3 cases the drainage worked perfectly but in the last the drainage only worked for two to three days. A kink had occurred in the tube where it left the spine, while one of the appendices epiploicæ had wrapped itself round the peritoneal button. We were unable to decide which of these two faults was the primary.

Our work on the obstructive type of hydrocephalus is not yet adequately developed for discussion but I feel the provincial pædiatric centres could take a larger part in the treatment of hydrocephalus; unlike the large neurosurgical centres they are not flooded with urgent brain tumour cases which must take first call on beds. Obviously our numbers so far are very small, but they do show that work of this nature can be carried out in a provincial general hospital.

There has been too little research on the natural history of the hydrocephalic child to determine the likely course in those who are labelled "hopeless", and it still seems impossible to forecast the case which will have a natural arrest. Recently I have been surprised by observations on two hopeless cases of obstructive hydrocephalus. One was an infant of 6 months who developed meningitis due to the *B. coli* and *Str. fæcalis* while on continuous intraventricular drainage. This child, instead of becoming more hydrocephalic during the period of the meningitis became less so and the vast head almost collapsed for a time. Possibly this was due to a reduction in the production of C.S.F. consequent on the meningitis though for a time we did wonder whether the organism could be manufacturing its own streptokinase and that this was dissolving some fibrinous obstruction.

The other child was started on daily ventricular punctures and after two of these the fontanelle became increasingly sunken and remained down without further punctures for about two weeks. It seems reasonable to suppose that in this child the vicious circle of increased pressure in the ventricular system had been broken, so that those absorptive mechanisms which still existed were able to function for a time.

Another problem with this subject is the relative lack of post-mortem material since the bulk of these children die at home. For this reason I feel that a research worker could visit all the pædiatric centres so as to keep in touch with their hydrocephalic patients and watch the results. By following up the cases and ensuring post-mortems he would obtain better information on the relation of head size and thickness of cortex to future intellect and learn to know better how to pick those cases which are likely to arrest spontaneously.

The work in Plymouth is being carried out by a team whose other members are Mr. Peter Childs, Mr. Michael Salz and Dr. James Smith.

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Mr. G. H. Macnab: 160 cases of hydrocephalus occurring in infancy have been fully investigated and operative procedure has been carried out in 105 cases.

Clinical estimation of tension in the anterior fontanelle as a sign of progressive hydrocephalus is unreliable. I have noted in my cases that clinical recognition of tension in the anterior fontanelle is not present until the ventricular pressure measured in the horizontal position is in the neighbourhood of 250 mm. Many cases have shown rapid enlargement of the head where the ventricular pressure ranged from 110 to 180 mm. In cases of progressive hydrocephalus, where there is communication between ventricular and spinal fluid, ventricular pressure ranges from 50 to 180 mm., as against a ventricular pressure of 250 to 300 mm. and over, in cases of intraventricular block.

O'Connell has shown that with an average spinal pressure of 120 mm., 80 mm. of that pressure is a variable factor, dependent upon changes occurring in the cardiac and respiratory cycles. This means that the cerebrospinal fluid has a thrusting force which can easily push out the poorly developed and un-united skull bones.

Fundus Oculi

In my series of cases papillœdema has never been observed, while excessive pallor of the discs is always present beyond the level seen in the newborn. The ophthalmologist will often label the condition as primary optic atrophy, but in my cases it is not associated with loss of vision. I find that the onset of blindness is usually a sudden event and occurs in the terminal stages of hydrocephalus. The main point to note is that in 7 of my cases of *suspected* hydrocephalus, where the ophthalmologist has declared the ocular media to be clear, progressive hydrocephalus has not developed.

I now turn to a small group of cases where the infant is seen with a "flat top to his head" associated with a wide anterior fontanelle. The circumference of the head is above normal for his age, but the eyes look straight ahead. Encephalograms show air passing over the cortex. Ventriculograms show a varying degree of dilatation of the ventricular system, and in some cases the ventricular pressure has been as high as 240 mm.

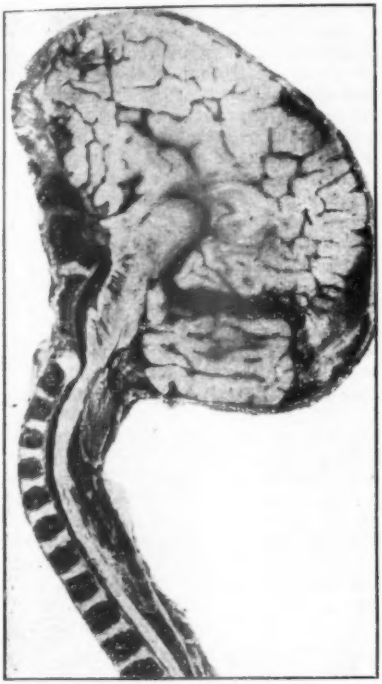
In this group of cases we seem to have imbalance between rate of formation of cerebrospinal fluid and its absorption, and it raises the question of the absorptive mechanism of cerebrospinal fluid. Arachnoid villi cannot be identified in the infant until the eighteenth month of life, and from studies of dye absorption I think these villi act only as a specialized mechanism to provide a greater absorptive area in the venous sinuses. The main absorption of cerebrospinal fluid is through the vessels around the subarachnoid space, the spinal surface accounting for one-fifth and the cerebral surface for four-fifths. It would appear, in this small group of cases, that balance is struck at a high cerebrospinal fluid pressure and hydrocephalus arrested. This means that we must still consider the question of failure of absorption in relation to the rate of secretion.

Arrest of Hydrocephalus

In my series of 160 cases 57 appear to have undergone arrest. Analysis of cases shows natural arrest 19 cases, flat top to head 5 cases, and operative procedure 33 cases. I had hoped, under the heading of natural arrest, to gain evidence that the hydrocephalus was due to inflammatory adhesions forming in the subarachnoid space, and then recanalization taking place through the thrusting force of the cerebrospinal fluid; but evidence is not forthcoming. On the other hand, we do know that natural arrest can take place by rupture of the ventricle through to the subarachnoid space, but by the time the rupture on to the cerebral absorptive surface occurs, the condition is in an advanced state.

Arnold-Chiari Malformation

Forty cases out of a total of 160 cases were due to this condition. In my series of cases, where there is clinical evidence of the presence of a myelomeningocele, hydrocephalus will be present or will develop in 50%. Dr. Cameron has offered an explanation for the time



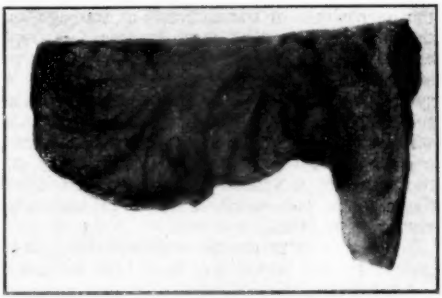


FIG. 2.—Small Arnold-Chiari malformation not giving rise to obstruction. No symptoms.

←FIG. 1.—Large cervical tongue—no hydrocephalus, no plug-like action.

of onset of hydrocephalus: (*a*) An Arnold-Chiari malformation may be associated with a block at the aqueduct of Sylvius or the foramina of Magendie and Luschka so that hydrocephalus is present at birth. (*b*) The cerebellum may not only herniate into the cervical spinal canal, but also up through the tentorial notch, so cerebrospinal fluid circulation is interfered with. (*c*) Venous congestion over the malformation can slowly set up arachnoiditis leading to blockage of the subarachnoid space. This last state accounts for the late development of hydrocephalus, and failure of its relief by decompression operations.

Investigation of an Infant Suspected of Progressive Hydrocephalus

Gas and oxygen is administered with the infant intubated. A Harris lumbar puncture needle is inserted at the lateral angle of the anterior fontanelle or the open coronal suture to exclude a chronic subdural hæmatoma. If a hæmatoma is suspected and the result is negative, a burr hole must be made in the temporal region, as the upper edge of the hæmatoma often fails to reach the lateral angle of the fontanelle. The infant is then turned into the left lateral position and left needle passed into the ventricle. Lumbar puncture is then performed and two Greenfield's manometers attached to spine and skull, and pressure measured in the horizontal position. Tilting of the table is used to give evidence of communication between cerebrospinal fluid in ventricle and spinal subarachnoid space, but this may be fallacious in advanced cases, as the cerebrospinal fluid is then contained in an elastic bag, which responds to gravity, and presses on the cisterna magna increasing the pressure in the fine spinal column of fluid. Simultaneous aspiration of cerebrospinal fluid from ventricle and replacement injection of oxygen into the spinal canal will always bring oxygen into the aspirated ventricle in true cases of communication between spine and ventricle; but the injection of 1 c.c. of neutral phenolsulphonphthalein dye into the ventricle, and its recovery from the spinal canal, may give negative results in the presence of communication, owing to dilution and stagnation in the ventricles, and slow rate of flow of fluid from spinal canal. In one case, 160 c.c. of cerebrospinal fluid was aspirated from the spinal canal with air replacement into the ventricle before the presence of the dye injected into the ventricle could be detected in the recovered spinal fluid. Dye tests of this type, if positive, show evidence of communication but if negative do not prove non-communication.

Accurate localization of the level of the block by air studies is still a major problem, and evidence of air passing freely over the cerebral cortex is also difficult to obtain. Owing to

the narrowness of the channels at this age, air-locks readily occur. Oxygen injected into the ventricles must be carefully traced through the whole of the ventricular system as far as the cerebral cortex. This requires great patience and many manipulations to free the air-locks. Ventriculography by this method will give good visualization of the ventricular system and basal cisterns, but gives no clear knowledge of the state of the cerebral subarachnoid space. If I have any doubt about the cerebral subarachnoid space I carry out encephalography, having reduced the ventricular tension by aspiration.

I am still not convinced that radiological evidence of a hold-up of oxygen at the level of the aqueduct of Sylvius or the tentorial notch denotes a complete block, for I have exposed the cerebral subarachnoid space in such cases and gained evidence of the presence of cerebrospinal fluid.

I turn finally to operative procedures I have carried out in an attempt to relieve hydrocephalus. 105 procedures have been carried out in 160 cases.

(*a*) 1929. *Bilateral ligation of common carotid arteries.*—8 cases. No improvement as the blood supply to plexuses of 3rd and 4th ventricle comes from the vertebral artery.

(*b*) 1937. *Diathermy of choroid plexuses of lateral ventricles.*—5 cases. No true arrest.

(*c*) 1950. *McNickle's blind procedure* of third ventriculostomy for aqueduct stenosis. 4 cases. One arrested for three years.

Third ventriculostomy under direct vision by lifting frontal lobe. 4 cases. Only temporary arrest obtained.

(*d*) *Ventriculo-pharyngostomy.*—Drainage of temporal horn of lateral ventricle into mastoid antrums through middle ear and down eustachian tube. 15 operations. An incision is made over the mastoid process and carried up on to the temporal bone. The mastoid antrum is opened and the aditus exposed. The roof of the antrum is then removed until the dura of the middle fossa is seen. A trocar and cannula is then passed into the temporal horn of the lateral ventricle and a polythene tube threaded into it. The lower end of the tube is turned into the aditus and the wound closed. It is interesting to note that leakage of the cerebrospinal fluid to the surface might occur for twenty-four hours but then seals off. In 15 cases of ventriculo-pharyngostomy 6 cases were arrested. 8 died at an interval of two to five months after operation. Only 1 infant died from acute ascending infection and 2 from meningitis at a later date. My main difficulty was blockage of the lower end of the tube by granulation tissue at the level of the aditus. These patients would drain from three to five months with an occasional block, which was relieved by a sudden burst of fluid through the nose. When all was well the fluid entering the pharynx was swallowed quietly and did not upset the child.

Communicating Hydrocephalus associated with the Presence of a Lumbar Myelomeningocele

The peritoneal cavity was opened and a hole drilled into the body of the vertebra overlying the sac, and a polythene tube passed blindly into the sac. I had hoped for collapse of the sac so that healing would take place, and for relief of the communicating hydrocephalus, but this procedure failed as the more the neural element present in the sac the greater the cystic loculation, due to fusion of layers of arachnoid carried up to the fundus of the sac by the nerves.

Spinal Theca to Ureter

The next procedure was to by-pass the sac by insertion of a polythene tube into the spinal space above the sac and into the lower end of the ureter through a lateral opening, having placed a proximal ligature around the ureter. The sac was noted to vary in tension, but 2 cases were admitted at three- and four-month intervals after the operation and died in a uræmic state. Post-mortem showed a severe hydronephrosis.

In the next 13 cases I removed the kidney and placed the tube direct into the ureter. When the cerebrospinal fluid pressure was high drainage took place, but eventually blockage or reflux infection occurred, as the tension on the pelvis of the kidney required to initiate peristalsis in the right direction had been replaced by a column of cerebrospinal fluid.

Ventricle to Dural Sinus

I now retraced my steps inside the skull and divided the superior longitudinal sinus at its anterior end and passed the polythene tube from lateral ventricle into sinus. Cerebrospinal fluid followed up the tube and blood did not reflux into the ventricle provided the child was quiet. Unfortunately, crying or laughing causes reflux of blood and eventually a clot develops in the tube. 7 cases were operated on. 3 appeared to be arrested over a period of two years. 4 died two to three months after operation.

I then placed a tube from temporal horn to sigmoid portion of transverse sinus hoping that the alternating suction force set up by respiration would prevent reflux of blood into the tube. 5 cases were operated on. 2 appeared to be arrested after a period of one year. One died two months after operation, blood-clot being present in the centre of the tube, the open ends being free.

Ventriculo-peritoneal Drainage

The next step was to pass a rubber catheter into the ventricle and attach it to polythene tubing, which was threaded subcutaneously to the right costal margin and then turned into the peritoneal cavity between the liver and the diaphragm and sutured into position. This area was chosen as there is no omentum present to block the tube and there is movement between liver and diaphragm. Out of 16 cases, 7 appear to have been arrested. 4 died one to eight months after operation. One died from acute ascending infection three days after operation, but this infant had an infected myelomeningocele. Fracture of polythene tubing by kinking at the time of insertion led to the use of polyvynyl tubing.

As I was not satisfied with this form of drainage I harnessed the lower end of the tube to the ureter. 7 cases were operated on and 2 were arrested. 4 died one to three months after operation. The chief danger in this operation is excessive loss of cerebrospinal fluid.

Ventriculostomy

The final attempt to-day is back inside the skull with a view to establishing a ventriculostomy as seen in some cases of natural arrest. Mr. D. M. Forrest, my Registrar at Westminster Children's Hospital, has devised a piece of apparatus (*see* Fig. 1 on p. 851) for providing drainage from ventricle to subarachnoid space.

In the past six months 16 cases have been operated on. Cases that have been tested at the end of three months show a big drop in ventricular pressure. 2 cases that had recovered from meningitis and showed evidence of thickened pia-arachnoid at operation have not arrested.

Professor Dorothy S. Russell spoke on the pathology of hydrocephalus, with illustrations. The substance of her communication will appear in the forthcoming annual volume of the Association for Research in Nervous and Mental Diseases (meeting held in New York in December 1954).

Dr. A. H. Cameron described his autopsy findings on 42 cases of hydrocephalus, of which 23 had been investigated at The Hospital for Sick Children, whilst he was Hydrocephalus Research Fellow there.

Post-inflammatory stenosis of the aqueduct was present in 7 of the 26 cases with spina bifida, 4 cases of post-hæmorrhagic hydrocephalus, and 2 cases of meningo-encephalitis. Congenital stenosis was present in 1 case with spina bifida and 1 case with encephalocele. Forking was present in 5 cases, all with spina bifida; in 2 of these there was superadded inflammatory stenosis and in 1 of the other 3 the aqueduct, though forked, was not abnormally narrow. Congenital stenosis or forking was not found in any of the cases without spina bifida or encephalocele.

There was conclusive evidence that the spina bifida lesion was in each case a myelocele. In the 6 neonatal cases dying within two weeks of birth the cord tissue presented on the surface of the sac as an unclosed neural groove; this was covered over by fibrogranulation tissue in the 4 cases dying within the first two months of life; and in the remaining 16 it was in much the same superficial position, but covered over by fibrous scar tissue and squamous epithelium.

In the cases of spina bifida there was a high incidence of diastematomyelia, rib deformities, deformities of the vertebral column underlying the sac and at higher levels, and of congenital abnormalities of the urogenital tract. This was considered to be the result of inhibition of Hensen's node during early embryonic life. Attention was drawn to the similarities between spina bifida in the human and experimentally induced spina bifida in amphibia.

Three cases of duodenal ulceration, all with gross internal hæmorrhage, were encountered. In each case there was a suppurative inflammation of the meninges and ventricular lining, involving the attenuated floor of the third ventricle. This was considered to support the neurogenic hypothesis developed by Harvey Cushing.

Mr. A. N. Guthkelch: 160 cases of infantile hydrocephalus have been observed in the Neurosurgical Department of the Royal Manchester Children's Hospital since 1947, of whom 90 were operated upon. In 30 cases the impression was formed and confirmed by a period of observation either that the hydrocephalus was too slight to need treatment or that it had become spontaneously arrested. A further 20 cases were rejected on account of excessive head size or grave general condition. Finally, 20 cases, all of myelomeningocele also presented with complete paraplegia. It has not been our policy to advise operation for hydrocephalus in these hopelessly crippled infants.

In the operated cases, clinical and radiological studies established the main types of hydrocephalus as follows:

Arnold-Chiari malformation	36 cases
Communicating hydrocephalus ..	31 „
Obstructive lesions of the iter of Sylvius	14 „
Others	9 „

In diagnosis we rely on ventriculography with air or Myodil. We have found the various forms of dye test misleading.

Each of these groups demands quite different methods of treatment.

(1) *Arnold-Chiari malformation.*—Mr. Macnab has enlarged upon the difficulties encountered in these cases. They probably arise because the obstruction of the C.S.F. pathways may arise at any of several levels in any one case, and often at more than one. There may be (1) stricture of the iter, (2) obstruction of the foramina of exit of the elongated fourth ventricle by compression of the elongated cerebellar tonsils and medulla within the cervical spine, (3) obliteration of the basal cisterns, and possibly (4) crowding of the hiatus tentorii from below, due to disproportion between the posterior fossa and the hind-brain.

At present we practise a posterior fossa decompression with sufficient of an upper cervical laminectomy to release the cerebellar tonsils. If there is obstruction of the iter we add a ventriculo-cisternostomy by Torkildsen's method; if subsequent excessive bulging of the decompression suggests blocking of the basal cisterns, we proceed to spinoperitoneal or ventriculoperitoneal drainage.

(2) *Communicating hydrocephalus.*—I agree that the majority of these cases can be related to birth trauma and to the effects of meningitis in approximately equal numbers. Seen sufficiently early (i.e. before the C.S.F. has returned to normal) some will respond to repeated lumbar puncture. Our operative methods have been mainly spino-ureteric and spinoperitoneal drainage. Both have been uniformly successful in achieving a permanent reduction in intracranial pressure with arrest of growth of the head, the fontanelle becoming and remaining concave. We find, however, that the spino-ureteric operation is followed by a substantially greater morbidity in the first few post-operative months due to chloride depletion and urinary infection: of 12 cases operated upon, 5 remained well for periods of six months to four years. In the spinoperitoneal group (13 cases) 10 remained well from three to eighteen months. These figures, together with one's natural dislike of the removal of a healthy kidney demanded by the former operation, have now led us to concentrate almost entirely on spinoperitoneal drainage.

(3) *Obstructive lesions of the iter of Sylvius.*—After a trial of third ventriculostomy without any permanent success (4 cases) we adopted Torkildsen's operation as a routine although it is a rather severe and technically a difficult operation in an infant. Of 9 cases so treated, 5 survive and have been completely controlled. We have also had 1 success with ventriculo-peritoneal drainage.

My conclusion is that given accurate diagnosis of the site of the obstruction and given also the strong tendency to spontaneous arrest which one sees particularly in the communicating group, it should be possible to achieve not less than 75% of surgical cures with long-term survival. But it must be emphasized that only follow-up studies such as those of Dr. J. E. Scarff can determine the final intellectual status of the survivors, and I think we shall be fortunate if the percentage of "useful citizens" exceeds 50.

Mr. Denis Browne: To understand the Arnold-Chiari deformity it is necessary to look at both ends of the infant, the feet as well as the head; and also to consider the mechanical conditions of the pregnancy that produced it. In the "closed shop" conventions of the modern organization of medicine the neuro-surgeon leaves the consideration of the feet to the orthopædic specialist, and both of them are uninterested in the mechanical conditions of the pregnancy, which is the province of the obstetrician. Babies with the Arnold-Chiari malformation of the brain emerge from pregnancies in which the mother has had a very small abdomen, with very little liquor, and abnormal discomfort. The feet are moulded into irregular forms of talipes, often fitting into each other as a coin does into the die that gives it shape. The brain is squeezed downwards into the foramen magnum by mechanical (not hydraulic) pressure on the skull, the necessary freedom for this movement being given by the expansible sac of the spina bifida.

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Mr. D. M. Forrest: *A Method of Drainage in Infantile Hydrocephalus*

I am convinced that it should be possible to preserve the integrity of the circulation of the cerebrospinal fluid in a high percentage of cases of hydrocephalus, and that drainage to other parts of the body or to the exterior should be reserved for those cases where no other course is open.

The main difficulties are:

Firstly, and most important, tubing in the subarachnoid space has a strong tendency to become blocked. Secondly, tubing tends to slip out of position when intraventricular pressure is released.

The first tendency may be minimized by using physiologically inert materials, by providing as large a surface as possible for the escape of fluid, and by devising a straightforward operative technique in which minimal disturbance of tissues and complete hæmostasis are easily attainable. The second danger is overcome by using a self-retaining tube.

Accordingly, I designed a drain embodying all these features.

It is made of nylon throughout. The outer end of the tubing is protected by a nylon disc 2 cm. in diameter and 3 mm. thick which lies flat on the cortex, and fluid escapes all round the deeply grooved periphery. The inner end of the tube is held in the lateral ventricle by its curled shape. This last feature is unnecessary in patients whose ventricles are comparatively small and in whom a reasonable thickness of cortex remains. For these I have made a straight-shafted tube. Both forms, with a stilette, are shown in Fig. 1. The shape of the

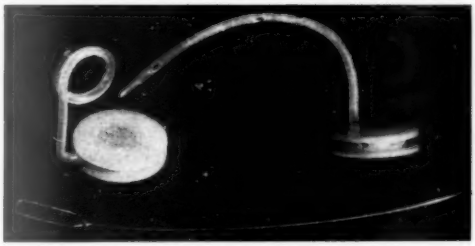


FIG. 1.—Drainage of hydrocephalus.

device has been planned for ease of insertion. A stiff stilette is passed through the tube to straighten it and the blunt closed end is passed through the cortex in the track of a brain needle. A 3 cm. incision in the dura and arachnoid permits the disc to be rotated into the subarachnoid space well away from the operative site.

Manufacture of the drain is simple. The disc is turned on the lathe from nylon rod. The tubing is shaped by passing a malleable stilette, bending as required, and subjecting it to heat before removing the stilette. About 110° C. is required for bending, so the device may be sterilized by boiling without losing its shape.

Mr. G. H. Macnab has performed the operation at the Westminster Children's Hospital twelve times in the past six months, and although 3 patients have already relapsed, the majority appear to be progressing well. Ventricular pressures and measurement of the head on the first 3 cases, taken three months after operation, show encouraging figures. All were cases of rapidly advancing hydrocephalus and all had ventricular pressures in excess of 300 mm. of C.S.F. Their pressures after three months were respectively, 50, 120, and 95 mm. In none of the 3 cases had the circumference of the head increased, and in one it was still 7·5 cm. below the pre-operative figure.

It would obviously be absurd to derive from these early results anything more than encouragement to test the method further, but I feel that some cautious optimism is justified.

In conclusion, I should like to acknowledge my deep indebtedness to Mr. G. H. Macnab for his constant advice and encouragement, and to thank Dr. S. A. Leader of Portland Plastics Ltd. for his help with the materials.

[*May* 2, 1955]

The Effect of Cerebral Palsies on Growth and Development

[*Summary*]

By BRONSON CROTHERS, M.D. [*Boston, Mass.*]

THE problem of the cerebral palsies in childhood is relatively simple. The emotional situation is usually met by authoritative and optimistic management and many people are involved in persistent training. The parents are supported by groups of therapists and tend to be comforted.

A very different situation may arise as the child grows older and as adult life is approached.

It has seemed to me that doctors in cerebral palsy clinics have been reluctant to face the fact that very little reliable evidence of the fate of the adult exists.

During the last few years we have been studying the long-term prognosis of these children. It has seemed to us that only two groups of patients, among the mass of cases defined as "cerebral palsy" of one kind or another, can be regarded as syndromes in the ordinary medical sense.

The children whose difficulties can be traced to kernicterus certainly have characteristic motor patterns and typical disorders of hearing and vision. The hemiplegic children also conform somewhat to type with sensory as well as motor difficulties. The rest of the children are highly irregular in symptomatology and mass prognoses are impossible.

It has seemed to us that the appraisal of these children must be based on the course of growth and development in the presence of anatomical, physiological, and psychological deviations.

In particular the distortion of development leads to difficulties in the achievement of independence and to complications between the child and the adults who are responsible for his care.

[Dr. Crothers showed a film illustrating various aspects of this admittedly complicated problem.]

[*May* 25, 1955]

DISCUSSION: JUVENILE RHEUMATISM [*Summary*]

Dr. E. G. L. Bywaters: *United States—United Kingdom Co-operative Rheumatic Fever Trial*

Dr. Bywaters, on behalf of the Rheumatic Fever Working Party of the Medical Research Council, gave a brief account of the background, planning and results up to one year of the co-operative controlled trial of cortisone acetate and aspirin in the treatment of rheumatic fever. The trial was organized jointly, in this country by the Medical Research Council and in the United States and Canada by the American Heart Association; a detailed account of this has been published (1955 *British Medical Journal*, i, 555). He added some comments based on the 87 children followed at the Canadian Red Cross Memorial Hospital, Taplow, and on a further series of early cases seen since that time, contrasting the results with others upon which other interpretations have been based. He indicated that a drug successful in the treatment of acute rheumatism has yet to be found.

Dr. Bernard Schlesinger: *The Changing Face of Rheumatism*

Dr. Schlesinger showed how the incidence of rheumatic fever had been falling since the turn of the century, and particularly during the last thirty years. With this, the severity of rheumatism seemed to have diminished, although this was more a clinical impression than a statistical fact. Possible reasons for this improvement were debated, including evacuation to the country, decline of streptococcal infections, less overcrowding and better diet. A combination of improved circumstances was considered to be mainly responsible, providing a more balanced diet and a better-nourished child population.

Some comparison was made between the clinical picture of rheumatic fever now and in the past, and also of the age group most likely to be affected, which had altered. Emphasis was laid on the many problems which existed fifty years ago and still remain unsolved. Diagnostic criteria were the same, but there had been some advance in prophylactic treatment with antibiotics. Surgery was now available to relieve progressive disability from mitral stenosis in adult life, but careful selection of cases was desirable.

The future was in the air. Although more benign at the moment, rheumatic fever might well relapse into its former virulence. There was little to suggest that the essential features of the disease had really changed.

Dr. G. T. Thomas: *Diagnosis of Rheumatic Carditis*

Dr. Thomas discussed the criteria on which the diagnosis of rheumatic carditis could be made early in an attack. Tachycardia was not as important or as common as had been stressed in the past: it occurred only in severe attacks and in nervous children. Enlargement was not an early sign but might develop after weeks or months of activity in a severe attack: any sudden increase in size was more likely to be due to pericardial effusion. Pericarditis, though certain evidence of carditis, was encountered in only 15% of cases; the PR interval was prolonged in only between 10 and 25%, depending on what criteria were used. Other ECG changes were not often helpful; the QTc was prolonged in only one-quarter of cases and T-wave changes were rare save in pericarditis. Early carditis could most often be diagnosed on auscultation; significant murmurs might occur within a few days of the onset of an attack. The subsequent course of these early cases, and others with more marked heart signs either from one attack or more, was shown over a follow-up period of three years.

Section of Psychiatry

President—W. MAYER-GROSS, M.D., F.R.C.P.

[*April* 19, 1955]

RECENT EXPERIMENTS WITH INJECTIONS OF DRUGS INTO THE VENTRICULAR SYSTEM OF THE BRAIN

Dr. W. Feldberg (National Institute for Medical Research, London):

Intraventricular Administration of Drugs in the Cat

During the last two years Dr. S. L. Sherwood and I have studied the action of various drugs injected into the cerebral lateral ventricle of the conscious cat[1]. For this purpose we screwed a metal cannula into the skull and kept it permanently in position sometimes for more than a year, without apparently producing any ill-effects. The tip of the cannula rested in the lateral ventricle; the butt, outside the skull, was closed by a cap with a rubber diaphragm through which the injections were made.

The drugs thus injected into the lateral ventricle will easily reach the third and fourth ventricles. The method does not allow strict localization of the action of the drugs to a specific region of the ventricular lining. In fact, through the lateral recesses and the subarachnoid spaces the drugs may also reach the surface of the cerebellum and cerebrum and be slowly absorbed into the blood stream. Nevertheless, the responses observed are mainly, if not wholly, effects of the drugs on the periventricular grey matter, or what the Germans call the "Zentralhöhlengrau". This region proved an as yet scarcely explored area of high pharmacological sensitivity.

In cats we found that with a number of different drugs injected intraventricularly recurrent patterns of reactions such as swallowing, salivation, retching, vomiting, and tachypnœa were obtained, but, in addition, a variety of drugs produced motor effects such as muscular weakness, inco-ordination, spastic paresis and general convulsions. Further, certain drugs caused dramatic changes in awareness and behaviour; the cats became drowsy, stuporous, catatonic, anæsthetized, or they became more alert or hostile. Some of the disorders produced in this way bore a close similarity to phenomena seen in mental patients. By describing some of the main effects seen after such injections, a good illustration is given of the variety of reactions obtained with different drugs and of the wide problems arising from this approach to the pharmacology of the central nervous system.

A few micrograms of acetylcholine elicit, within a few seconds after the injection, a peculiar high-pitched cry, or retching. The cat then sits down on its hind-legs with head tilted and eyes half shut and remains immobile for a few minutes. The condition resembles an akinetic seizure. During the following hours the cat is subdued and stuporous. With larger doses of acetylcholine there is a short period of generalized convulsions, followed later on by deep stupor with catatonic features.

Catatonic stupor is also a typical late effect of anticholinesterases such as eserine or di-isopropylfluorophosphonate (DFP) when injected intraventricularly. The first effect after an injection of eserine or DFP, however, is characterized by vigorous scratching, wiping of the face, licking, gnawing the paws, washing, shaking the head and twitching the ears. The cat behaves as if it experienced the sensation of itching. This itching is a central effect of the anticholinesterases and was sometimes observed with acetylcholine as well. Apart from the motor effects associated with itching, the anticholinesterases cause changes in stance, gait, and posture, as a result of increased motor activity, before stupor and catatonia develop. In this condition, the cats can be put in abnormal postures which they retain for many seconds or minutes. Nevertheless, they are capable of normal movement, for when the cat has remained for some time balanced across the rungs of an upturned stool a gentle push from behind causes it to jump down in its usual well co-ordinated manner.

A different condition of impairment of consciousness or awareness from that produced by the anticholinesterases and acetylcholine occurred after intraventricular injection of the sympathomimetic amines, noradrenaline and adrenaline. In doses of less than 100μg. they

[1] A more detailed description of these experiments, their discussion, and the relevant references are found in the following papers: Feldberg, W., and Sherwood, S. L. (1954) *J. Physiol.*, **123**, 148; (1954) **125**, 488; (1955) *Brit. J. Pharmacol*, **10**, 371.

produced a condition resembling light nembutal anæsthesia. A similar effect had previously been described, by Leimdorfer in America, on cisternal injection of larger doses of these amines.

These changes produced by the anticholinesterases, adrenaline and noradrenaline, are changes of depression or impairment of consciousness or awareness, and it is interesting that this region which we flood pharmacologically is generally associated with consciousness. For instance, electric stimulation of certain points immediately under the surface of the third ventricle, i.e. the massa intermedia, produces sleep, as shown by Hess. Further, it is well known that tumours pressing on this region cause unconsciousness in man.

Atropine, on the other hand, produced increased liveliness but with signs that the cat's appraisal of its surroundings was impaired.

With a number of drugs injected intraventricularly, the motor phenomena were predominant. Sherwood and I found that hexamethonium and histamine produced muscular weakness; Banthine, muscular inco-ordination; decamethonium, spastic paralysis; and +tubocurarine, in an amount of as little as 30 μg., general convulsions resembling major epileptic fits, during which the animals were apparently unconscious. The +tubocurarine convulsions are of particular interest to the theory of subcortical origin of epileptic seizures, because of the ability to simulate seizure-like activity by drugs acting from subcortical regions.

The finding that the anticholinesterases when injected intraventricularly into cats produce signs of severe itching is relevant to the phenomenon of itching in general. It is interesting to recall that cats may act in a similar way on electrical stimulation of certain structures of the mid-brain. Hess found that cats acted in this way on stimulation of the nuclei of the septum pellucidum as far ventral as the anterior commissure and in a region immediately above and behind the mammillary bodies, i.e. structures bathed by the ventricular fluid.

When discussing the physiology of itching we have thus to distinguish between itching originating in the skin and itching of central origin. The main physiological stimulus for itching in the skin may well be the release of histamine in the skin, and it is therefore not surprising that itching is a well-known feature of the effects of histamine liberators in man. It will not always be easy to assess whether the itching produced by administration of a drug is a central or a peripheral effect. Morphine, for instance, is a histamine liberator but also causes signs of itching on cisternal injection. Therefore the well-known pruritus in man after administration of morphine may in some cases be of peripheral origin, in others of central, and again in others a combination of both mechanisms. There are other clinical observations of itching which are unlikely to be due to primary skin conditions and where the itching is central in origin, for instance the itching of lichen planus, since it is so dramatically relieved by lumbar puncture and removal of a few ml. of cerebrospinal fluid.

Stupor and catatonia appear to be characterisitic features of the presence of acetylcholine and anticholinesterases in the ventricular system. Since catatonia occurs in some forms of schizophrenia it is interesting to note that other attributes characteristic of this mental disease have been described in response to anticholinesterases. DFP was tried in America by Grob, Lilienthal and Harvey, and in England by Rowntree, Nevin and Wilson, in the treatment of myasthenia gravis, but the patients refused the continuation of daily intramuscular injections of DFP because they led to insomnia, nightmares, mental confusion, and hallucination. In addition, Rowntree *et al.* found that DFP produced in a number of schizophrenic patients an activation of the psychosis or the reappearance in chronic cases of the florid symptoms which had characterized the onset of the illness. If we assume that the catatonia produced on intraventricular injection of anticholinesterase is the result of cholinergic neuronal activity or excess of acetylcholine in the region of the periventricular grey—and it is difficult to avoid this conclusion—then it may well be that the hallucinatory and other phenomena seen in patients after DFP are also due to its cholinesterase inhibiting effect in the mid-brain.

Several drugs are known to produce catatonia in animals on subcutaneous injection. The best-known drug of this kind is bulbocapnine. Sherwood and I found that on intraventricular injection in cats it brings about a state of catatonia in doses a fraction of those required to produce this effect by subcutaneous administration. The relative smallness of dosage and the speed with which the bulbocapnine effects appear with this route of administration seem to indicate that structures close to or directly in contact with the ventricular surface are likely to be implicated. This indication is borne out by comparison with results obtained by lesions of selected anatomical sites in the mid-brain close to the ventricular lining. From these, and only from these sites, catatonic effects analogous to those of bulbocapnine are obtained, as shown by Ingram, Barris and Ransom, by Bailey, by Magoun, by McCulloch, Ridley and Sherwood, and by Hess.

Further, in doses (100–200 μg.) even smaller than those needed to produce consistently signs of catatonia, bulbocapnine caused changes in behaviour or "character" of the animal

which lasted for about half an hour. A previously friendly and affectionate cat, when approached in this condition, lashed its tail, tried to bite, hit out with one or both front paws, sitting erect and hissing with bared teeth. Thus, a striking although short-lasting change in behaviour occurred in response to a drug which again probably acted on the periventricular grey matter.

In animals, the main method of obtaining the syndrome of catatonia, apart from drugs, is the placing of lesions in the upper brain-stem. This raises the question of whether the drugs bulbocapnine, the anticholinesterases, and acetylcholine also produce a kind of pharmacological lesion by paralysing nerve cells and thereby interrupting some specific pathways, in analogy to the paralysing effects of acetylcholine (or nicotine) on peripheral structures when producing block of synaptic transmission in a sympathetic ganglion, or neuromuscular block.

Finally, when discussing the action of adrenaline and noradrenaline in producing a condition resembling light Nembutal anæsthesia, we have to realize that noradrenaline is a normal constituent of the central nervous system. Vogt has recently mapped out its distribution in the dog's brain. Highest concentrations were found in the diencephalon, the mesencephalon, and the medulla oblongata; in fact, in those regions of the brain on which the noradrenaline probably acts when producing the condition resembling light anæsthesia. The region mapped out by Vogt for high concentration of noradrenaline closely resembles Magoun and Jasper's arousal area in the reticular formation in the brain-stem, and this naturally raises the question of whether noradrenaline normally influences our state of awareness by being released in this region. From its distribution in the brain and its central action one is, in fact, tempted to postulate for noradrenaline an important central function, that of exerting an influence within the reticular activating system. Noradrenaline may not be the only substance acting in this way; other pharmacologically active substances present in this region—for instance, Amin, Crawford and Gaddum have shown that the distribution of 5-hydroxytryptamine in the brain follows fairly closely that of noradrenaline—may act on or through this system. Several of the effects Sherwood and I observed on intraventricular injection, on the sensorium as well as on the motor side, may finally find their interpretation on these lines.

In conclusion I want to stress that the gap we are trying to span between pharmacology of the central nervous system and mental disorders is still one which has to be crossed with the utmost caution: there are danger signs facing us at almost every step.

Dr. S. L. Sherwood (National Institute for Medical Research and Severalls Hospital, Colchester, Essex):

The Response of Psychotic Patients to Intraventricular Injections

An attempt was begun five years ago to treat chronic catatonic stupor by intraventricular injection of drugs. The reasons for employing this particular method and its early results have been described in *Brain* (Sherwood, 1952).

The particular methods of observation and recording employed were selected with the hope of discovering the influence of treatment on the patients' particular signs, symptoms and disabilities; for this reason patients with unequivocal syndromes were selected in the first place and a number of relevant tests and observations in the field of pathophysiology had to be sacrificed for lack of facilities and man-power.

In all 26 patients had intraventricular injections (5 of these were treated at Manteno State Hospital, Illinois). In the early cases the injections were given with sharp needles through the scalp and previously made frontal burr holes; more recently this was done with fine hypodermic needles through the scalp and rubber-bung of a cannula screwed into the frontal bone; with either method the frontal horn of the ventricles was reached (Fig. 1).

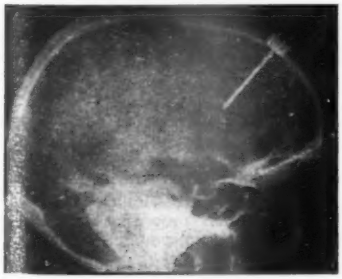


FIG. 1.—Lateral skull X-ray showing permanent intraventricular cannula in position.

Early on, distilled water was used as a vehicle, later saline, and recently Tyrode's solution which contains a pH-buffer system; distilled water itself has an effect on the patient of shock which may last several hours. The volume injected varied from 1 to 10 ml., and in the case of saline, or Tyrode's solution, appears to have no effect of its own, provided the intraventricular pressure is not significantly altered. This was secured by allowing an equal amount of C.S.F. to drain off through a second needle.

The initial drug doses were calculated as that proportion of the systemic dose which would be contained in the ventricular fluid if the distribution after systemic injection were even throughout the body.

All cases treated in this series were chronic psychotics. In the Severalls Hospital series the illness had lasted between three and twenty-five years—average 10·7 years. The ages, diagnoses and duration of illness in all cases are displayed in Tables I and II; the Tables also show where surgical treatment has been carried out.

TABLE I.—THE EFFECT OF INTRAVENTRICULAR INJECTIONS OF ChE, SEROTONIN AND C5 ON CATATONIC SCHIZOPHRENICS

CATATONIC STUPOR AS MAIN SIGN.

Name	Age	Δ	D	S1	S2	Can	Best Drug	Others	Impr	Reactivity to Environment Scale 0-5 Before	After
E.B.	37	C.S.	8		+		C5×3	1	+	0	2
E.R.B.	43	C.S.	16		+		ChE×3			1	1
M.B.	29	C.S.	9			+	S×37	12	+	0	2
D.C.	46	C.S.	18			+	ChE×24	13	+	1	2
Den.C.	29	C.S.	9			+	S×12	26	+	1	3
E.F.	35	C.S.	4	+			B×4		+	1	4
S.G.	27	C.S. (HI)	12			+	S×16	43	+	0	4
R.G.	20	C.S.	4	+			ChE×5	4	+	0	4
A.L.	39	C.S.?	9	+			ChE×8		+	0	2
H.M.	30	C.S.	4		+		ChE×6	14	+	0	2
D.R.	41	C.S.	8		+		Cs×3	3	+	0	3
E.S.	31	C.S.	7			+	ChE×32	18	+	0	5
H.W.	27	C.S.	12		+		ChE×9	8	+	2	4

TABLE II.—THE EFFECT OF SEROTONIN, BANTHINE, ADRENALINE, C5 AND ChE ON OTHER TYPES OF PSYCHOSES

OTHER LEADING SIGNS MAINLY EXCITEMENT

Name	Age	Δ	D	S1	S2	Can	Best Drug	Others	Impr	Reactivity to Environment Scale 0-5 Before	After
JoanB	32	P.S.	3	+	+		S×5	2	+	3	5
JoyceB	32	D.P.	12	+			B×5	5	+	1	3
D.H.	30	D.P.	10		+		(Ad ChE)			1	1
V.J.	30	S.S.	8	+			B×9	1	+	0	3
H.S.	40	S.S.	25				Cs×7	2	+	1	5
F.S.	41	FME (HI)	20				Ad×3		+	4	5
J.T.	34	D.P.	17				ChE×1	15		2	4
L.T.	24	D.P.	3	+			ChE×3	2	+	0	4

Abbreviations for Tables I and II

Δ = Diagnosis.
PS = Paranoid Schizophrenia.
DP = Dementia Præcox.
SS = Simple Schizophrenia.
FME = Familial Myoclonic Epilepsy.
HI = Head Injury.
CS = Catatonic Schizophrenia.
D = Duration.
s1 = Surgery before injection.
s2 = Surgery after injection.
CAN = Permanent indwelling cannula.

Scale of reactivity in arbitrary units.
0 = Complete inaccessibility.
5 = Behaviour approaching normal.
× number = Number of injections.

Tables I and II, representing a summary of all the cases treated. It will be noted that wit three exceptions all patients did show improvement and that the performance of a leucotom either before or after a course of injection treatment, had no decisive effect on the result c injection treatment.

The injections were spaced at daily to fortnightly intervals according to persistence of effects and the patient's needs. In all 366 injections have been given; the largest number in any one case was 59 injections, and the smallest number 3. All except 3 patients had more than one drug, given at different times. In several cases control injections of distilled water, saline and Tyrode's solution were given with no clear-cut effect; the difference in drug effects themselves provided further satisfactory proof of the causation of the changes.

During the last two years all cases were controlled and followed up with extensive EEG recordings.

I shall now report the effects of the individual drugs, first stating the immediate effect and, second, the long-term effects.

Adrenaline HCl. 5 patients received this drug. 4 were chronic catatonics, one was a case of familial myoclonic epilepsy. The effects when given intracisternally in doses of 0·5–2 mg. have been described by Leimdorfer (1950) and by Leimdorfer and Metzner (1949) in non-psychotic patients and animals and for noradrenaline by Feldberg and Sherwood (1954) given to cats intraventricularly, as those resembling sleep or anæsthesia.

In the present series 4 patients received 2 to 4 successive injections of adrenaline HCl in doses from 5–250 μg. dissolved in 1 to 5 ml. saline or, in one case, Tyrode's solution. In all four cases, and with all doses tried, adrenaline produced a general relaxation and lowering of muscle tone, but no apparent weakness; this was associated with a transient flush of the face and warming of the limbs; later, especially with higher doses, the patient may sweat and his face may become pale, although his skin remains warm. Nausea and vomiting occurred in 3 patients who received the drug in saline; of the other two, one, a catatonic of over twenty years' standing and showing advanced deterioration, showed little sensitivity to cholinesterase also, and the other—the case of familial myoclonus—received his injection in Tyrode's solution, i.e. the acid drug in a buffered solution.

Within ten to thirty minutes, depending on the dosage, all patients became drowsy and dozed or slept; they were all easily aroused; the previously inaccessible schizophrenics showed understanding by answering simple questions rationally, with the one exception just mentioned; before they became drowsy they would utter short remarks spontaneously and appropriately. This stage was brief and usually too short to explore the possibilities of a lengthy conversation. This stage of drowsiness began to wear off after fifty minutes with the smaller and after two to three hours with the larger doses; a gradual reappearance of the previous signs and symptoms occurred over the next twelve hours; for the next day or two the patients were a little more active, showing less rigidity in their behaviour patterns but they were also more liable to obey sudden or violent impulses.

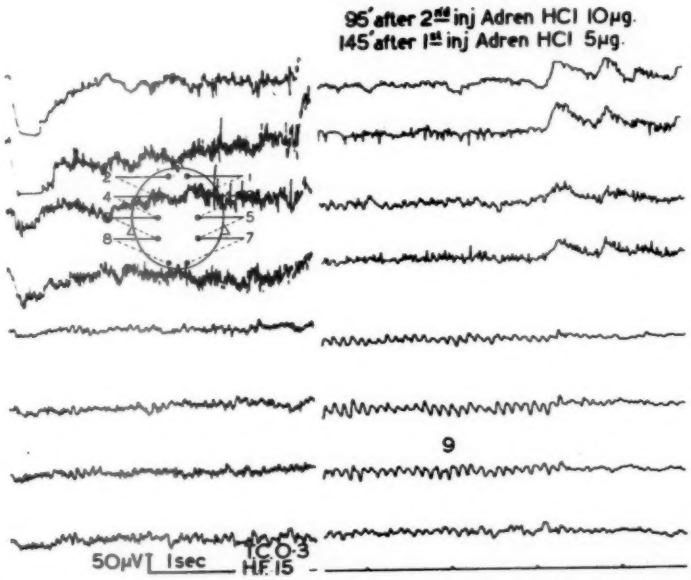


FIG. 2.—EEG 30-year-old patient, dementia præcox. Left, control record; right, after intraventricular adrenaline; switching as on inset diagram.

The patient suffering from familial myoclonic epilepsy (von Unverricht's disease) reacted similarly but he was a much better witness: he became sleepy only after forty to fifty minutes, some twenty minutes after the EEG had begun to show features associated with sleep. Five minutes after the injection, on three occasions, he fancied he had passed urine—but this was in fact not so; he also experienced slight transient nausea with 50 μg. of adrenaline, and none with 15: in either case the spasms and twitches were absent or markedly reduced, and he was less spastic for two to three days.

In the case of the schizophrenics the EEG showed the following changes: if there was no alpha rhythm in the control record, a regular rhythm appeared within 30 seconds to a few minutes (Fig. 2). When an alpha rhythm had been present before injection, it was greatly enhanced, and in either case, after a transient increase in frequency during the first few minutes, it dropped to a lower rate. At the height of the drug effect the records were very similar to a typical light sleep record, particularly one obtained with the aid of barbiturates. In the case of familial myoclonic epilepsy, there was a great reduction of spikes and irregular slow waves and also, of course, of the twitch artefacts (Fig. 3).

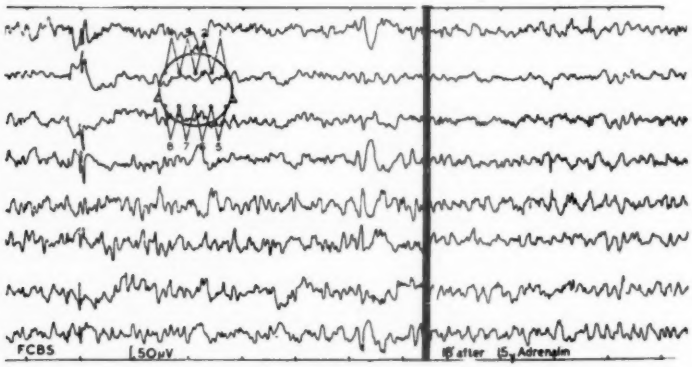


FIG. 3.—EEG 41-year-old patient, myoclonic epilepsy. Left before, right after intraventricular injection of adrenaline. Note reduction of spikes and complexes.

Atropine.—The trials with atropine were inconclusive and limited. 3 patients had doses of 250–500 μg. of atropine sulphate in saline; it produced an increase of spontaneous movements of a relaxed kind—often they consisted of stretching of limbs, and the patients were ready to smile or giggle although two of them certainly were not in the habit of doing so otherwise. The effects on the EEG are shown in Fig. 4.

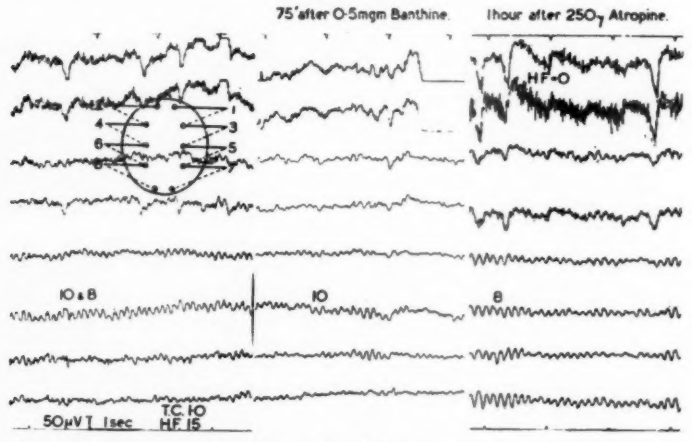


FIG. 4.—31-year-old catatonic schizophrenic. Left before, centre after intraventricular injection of Banthine. Right, after atropine.

Banthine and Probanthine.—This drug (β-diethylaminoethyl xanthene-9-carboxylate methobromide) has, in addition to an atropine-like effect, a blocking action on autonomic ganglia, and in large doses on the neuromuscular junction. 11 patients received this drug in up to 19 successive injections; 9 were catatonic schizophrenics, one a well-preserved paranoid schizophrenic and one a simple schizophrenic.

Within about one hour of each injection all patients became more active: this concerned both "spontaneous" behaviour, and reactions; with larger doses—500 μg. or more—catatonic patients would become overactive and show emotional stress, especially patients who were hallucinated or under the influence of harassing delusions, so that they displayed impulsive and sometimes even violent outbursts; some became very agitated by them and injections of Banthine were discontinued; most of them became capable of expressing themselves and of describing their state well—especially those with paranoid trends; even those who spoke only gibberish became garrulous. During a course of injections at weekly intervals for five to ten weeks it appeared that some patients who suffered from delusions and hallucinations became conscious of the abnormality of their experiences, but did not lose them: their affective capacity was more influenced than their thought processes. The effect of a single Banthine injection persisted for up to one week; some patients showed a general improvement after the end of a course of injections which far exceeded their state before treatment, and this improvement endured for up to four or six weeks after the last injection—especially in those who before treatment were little disturbed by their hallucinations or delusions. The only consistent physical signs were a general improvement of complexion and, with doses of 500–1,000 μg., slight muscular weakness for two to three hours after injection.

The EEG again showed a change in the number of alpha frequencies if several had been present before—usually an intermediate or slightly faster one became more prominent; rhythms of the beta range increased and became clearer and complexes within the delta range also became prominent for the first few hours after each injection (Fig. 4).

Cholinesterase.—This enzyme, which hydrolyses acetylcholine, is difficult to obtain and purify. Originally freeze-dried human erythrocyte stroma was used; later an extract of the electric organ of electric eel was used. One ml. of this was capable of hydrolysing 4 grams of acetylcholine per hour; latterly a preparation from human erythrocytes in which the active fraction had been detached from the stroma and thus become water soluble, was used; it had a Q ACh. of 126. 15 schizophrenics received between 1 and 32 injections of cholinesterase.

The earlier preparations had undesirable immediate results; they caused a good deal of nausea and vomiting and a fall in blood pressure; the electric eel preparation was better than this although less efficient also on the state of the psychosis with the passage of time; the most recent preparations freshly made up from dry powder in Tyrode's solution instead of saline or distilled water produced few or none of these signs; a slight sensation of nausea was easily counteracted by 3–5 grains of Chloretone given half an hour before the injection.

The effect of cholinesterase became noticeable within the first minute after injection; the patient becomes flushed and increasingly accessible; fully catatonic patients begin to react and within one to three hours they respond to instructions or reply to simple questions; they may eat and look after their own needs. One patient, in a perpetual state of violent paranoid excitement and confusion, calmed down within two hours and became co-operative and spoke rationally. This clinical general improvement may continue from one to three weeks after a single injection, especially if larger doses are used; usually injections were given at about weekly intervals. Of the 15 patients treated 6 improved at one time or other to behaviour approaching normal, and this persisted for four years in one case, and for two years in another without further injections. However, both these patients had had a leucotomy one and two years respectively before injection treatment; in others the improvement would not outlast the last injection by more than four weeks. Only 2 patients showed no certain improvement. All others became more, if not fully, reasonable and co-operative and alert. 2 became depressed, agitated and tearful—possibly because of their increased alertness and insight—and it was thought wiser and kinder to discontinue injections and proceed to leucotomy, especially since the supply of cholinesterase was insecure at the time.

In the EEGs, the alpha rhythm was greatly enhanced and stabilized at a frequency usually higher than the lowest previously shown; only in one case, with an original rhythm at 12 c/s, was there a drop. The higher rhythms of the beta range tended to slow down and lose

amplitude and tended to disappear in the favourable cases. Complexes or delta rhythms appeared rarely following cholinesterase injections (Fig. 5).

Pentamethonium Iodide, a myoneural blocking agent, had an effect similar to cholinesterase but less marked and never enduring for more than twelve to thirty-six hours; nausea was absent; *Flaxedil* also resembled this kind of action. The doses used were 150 and 300 μg. respectively per injection.

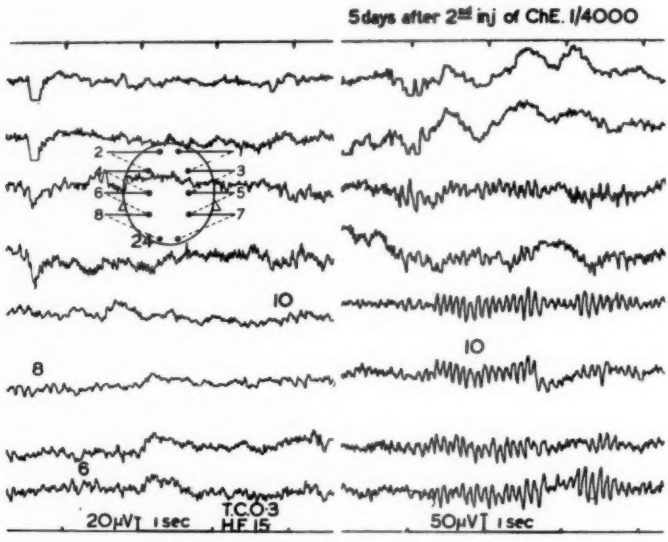


FIG. 5.—29-year-old catatonic schizophrenic. Left before, right after intraventricular injection of ChE. Note the change in α frequency.

Hyaluronidase was given in 5 cases in saline by itself and in 8 cases combined with other drugs (cholinesterase, C5, Flaxedil) on the speculation that tissue permeability might be improved; no definite conclusions were obtained. The doses used were 300–500 μg.

Serotonin.—The neurotropic effects of this drug have been described by Woolley and Shaw (1954) and Amin *et al.* (1954) who showed that it is a potent antagonist to lysergic acid diethylamide and that the mid-brain *naturally* contains 5-hydroxytryptamine.

4 patients received this drug in doses of 15 to 75 μg. Within a few minutes of the injection the patients begin to yawn and clear their throats with increasing vigour and loudness; after an early flush the patients become pale and perspire; one patient vomited without nausea; the pulse-rate tends to drop; gradually, over the next one to three hours they become more active or even restless; they talk readily and make contact easily although there is no early effect on their thought processes; one patient sang and shouted for many hours; nevertheless there was no evidence of distress. Over a period of weeks of two to three weekly injections they improve stepwise until they become employable and interested; personal habits improve also, they feed themselves more tidily, look after their personal toilet, their speech assumes increasing relevance, and they can spend their time to some extent as part of a community. The case of paranoid schizophrenia improved so much after 5 injections—the delusions appeared to have gone—that she was able to leave the hospital for home; however, she had had a modified leucotomy some eighteen months earlier and had never shown any degradation; she remained at home some three months before she had to return.

Treatment of 2 cases of dementia præcox had to be broken off—one because of a flare-up of phthisis and the other because of a C.S.F. infection. The case of catatonic schizophrenia has continued to be very well for two months after the last injection. In fact, the most striking improvement occurs early during a course of injections and after the end of it.

The EEG shows an increase of alpha amplitude but not frequency and a stabilization of the frequency with clinical improvement. There is, however, especially during the period

of transition and improvement, also a transient increase of delta waves and abnormal complexes; fast rhythms tend to disappear (Fig. 6).

There are some features that are—as in the animal experiments—common to all drugs used in this series: they include the changes in complexion which persist much longer than the mental changes after the drug; within the first few hours there may be nausea or vomiting, a drop in blood pressure, and during the first twenty-four to thirty-six hours there is often—

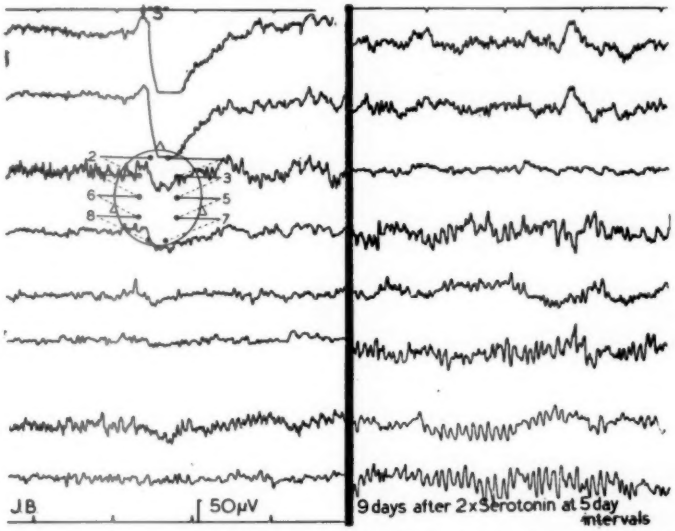


FIG. 6.—Response to EEG to repeated intraventricular Serotonin injections; 32-year-old paranoid schizophrenic. Note the increase of á waves but also the tendency to complex formation.

especially with cholinesterase—a rise in temperature which is not due to an infection. In general also, the C.S.F. pressure is related to the patient's mental health: it is low—often not exceeding atmospheric pressure in catatonics in the prone position—and it rises with improvement to normal levels of about 10 cm. of C.S.F. above the skull surface. Some women with amenorrhœa began to menstruate again.

Complications.—4 of the patients had epileptic seizures, but each time evidently the choroid plexus or a branch of the anterior cerebral artery had been punctured, for blood-stained fluid was aspirated: no fits ever occurred when the C.S.F. was clear.

Infections of the C.S.F. occurred in 3 cases—they were discovered through routine C.S.F. examination and were due in all cases to so-called non-pathogenic organisms. There was no difficulty in controlling the infections with antibiotics. None of the patients showed signs of ventriculitis or meningitis. Some of the cannulæ were removed for this reason; in other cases the cannulæ had to be reinserted because they were blocked by a gelatinous substance—especially in the earlier narrow-bore model.

On the whole, of the drugs most extensively tried, cholinesterase had the most marked effect on abnormal thought processes and hallucinations, Banthine greatly increased activity but reactions did not necessarily become more adequate to stimuli themselves; Serotonin has also a marked effect on activity and reactivity, though perhaps a slightly less marked effect on the quality of reactions. It appears to stand between cholinesterase and Banthine.

In the EEG records, there are some specific trends regarding the various frequencies usually displayed by patients within the schizophrenic group; it is, however, clear that well-being in any one patient is associated with a certain alpha frequency and a certain pattern of distribution of this rhythm; the recurrence, after discontinuation of injections, of the earlier pathological pattern goes stepwise with the state of the patient's mind. Thus, the EEG changes are specific both for the patient and the drug (Tables III, IV, V).

The method of intraventricular medication has not yet been used on recent or mild cases and on very few cases only who could describe well the sensations experienced on receiving an intraventricular injection.

The dosage of each injection and the spacing of them still represents serious difficulties; in the light of the Banthine injections, there can be no doubt that an overshooting of the

goal can occur; on the other hand, in the case of cholinesterase it happened twice that patients after a period of marked improvement and without further injections relapsed, going through a state of "oneirophrenia" in which further injections became technically impossible.

Two patients showed so little response to intraventricular injection of any drug that further injections were abandoned. One was a case of catatonic stupor in a woman aged

TABLE III.—INJECTION OF BANTHINE

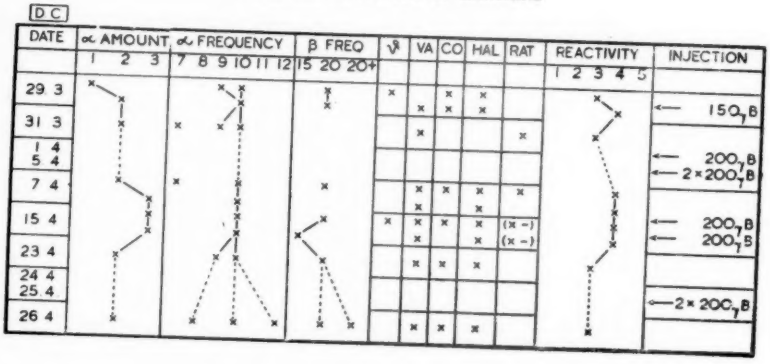


TABLE IV.—INJECTION OF CHOLINESTERASE

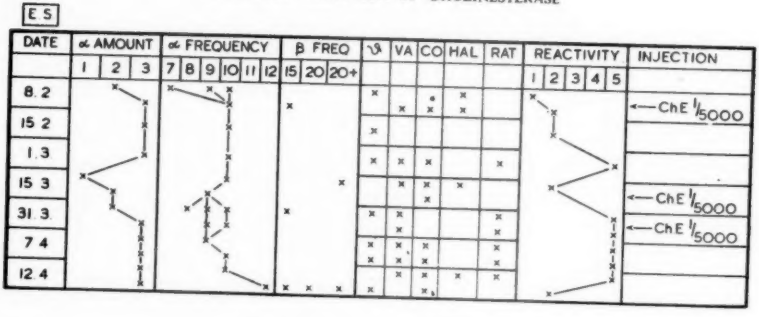
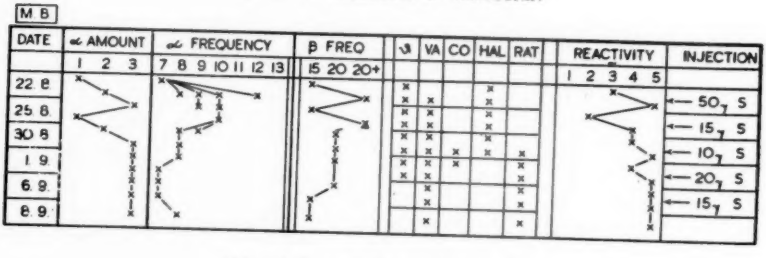


TABLE V.—INJECTION OF SEROTONIN



Abbreviations for Tables III, IV and V

θ = Theta waves.
VA = Response to visual attention.
CO = Complexes.
HAL = Hallucinations.
RAT = Rational behaviour.

Tables III, IV, and V, illustrating relationship between EEG and mental state. Note alpha frequency.

43 which had persisted for sixteen years. The other was a grossly deteriorated case of dementia præcox of ten years' duration (*see* Tables I and II).

The different effects of various drugs administered through the ventricles make it difficult, if not impossible, to deny that the results obtained must be based on a selective sensitivity of ependymal areas to different drugs. That the areas so greatly influencing behaviour should be accessible by this method is not surprising if one considers that Hess was able to obtain with electrical stimulation in cats integrated behaviour patterns in areas which are very close to the ventricular surface near the mid-line. It is especially the posterior subthalamic areas from which he has been able to obtain behaviour that included anger, aggression, irritability, mood swings and even movements which make it difficult to assume that they are caused by anything but a hallucination. Whether the primary lesion in the schizophrenic is a "lesion" or not, it is difficult to decide: we know, further, from the EEG and from recordings made from the mid-brain of cats which were made "catatonic" by lesions, that there are areas which are electrically hyperactive and not subject to modifications by external stimuli. It would be an attractive theory to assume that this hyperactivity is the result of "de-afferentation" from their normal sources, for it has been possible to compensate with cholinesterase to some extent for the effect of lesions in cats. On the other hand, exacerbation of signs can be brought about with acetylcholine (Sherwood *et al.*, 1952) in the ventricles or by systemic or intraventricular bulbocapnine (Ingram and Ranson, 1934; Feldberg and Sherwood, 1955). Recent work in which labelled isotopes were used (Sweet and Locksley, 1953; Roy John, 1954) has shown that the various constituents of the C.S.F. are produced and re-absorbed at differential rates and, moreover, that these rates may vary with the state of the animal. This information, together with the implications of selective sensitivity of certain cell groups, makes intraventricular injections a suitable tool for investigation and treatment in mental disorders.

In no two patients are exactly the same functions impaired. Indeed, mental illness often represents a picture of partial disorders. While, for instance, logical thinking as we know it may be absent the patient is still able to perform the majority of ordinary functions perfectly. In fact, any one set of functions may be picked out by the illness and disordered. Since definite behaviour patterns have been produced in animals by the action of drugs, it may be possible to counteract the malfunction of these by employing the appropriate drug locally.

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Dr. D. Richter: Though intraventricular injection is not in itself new, Dr. Feldberg and Dr. Sherwood, by their use of permanently implanted cannulæ, have made observation very much easier, and the systematic study of a series of drugs in this way represents a considerable advance.

This work has opened up a big new field for research. The effects of the drugs examined have so far been given mainly in qualitative terms, and there is clearly room for further quantitative experiments. This applies not only to measurements of metabolic factors and the electrical activity of the brain, but also to measurements of behavioural changes of the kind that can be made by a psychologist. It would be of interest, for example, to measure the effects of drugs administered in this way on the behaviour of experimental animals in conditioning experiments, and the effects on trained animals studied by a maze technique.

The number of different drugs available for study is enormous. Those chosen for investigation must therefore be chosen with some care. Of obvious interest are the so-called "fantastica", which act primarily on the higher centres of the brain. But more may perhaps be learned by studying the effects of specific metabolic factors such as enzyme inhibitors. In this way we may be able to learn more about the significance of the different biochemical processes going on *in vivo* in the brain. A few years ago it was commonly believed that the metabolism of any one part of the brain was much the same as that of another: only recently has it come to be recognized that different anatomical regions are specialized metabolically as well as in their physiological function. Biochemical differences in regions such as the substantia nigra and the red nucleus were suggested by the difference in colour; but more exact studies of the distribution of acetylcholine, cholinesterase, noradrenaline and other substances have shown that there are large and important differences in the metabolism of different parts of the brain. By the use of specific metabolic factors much might therefore be learned.

Apart from the new knowledge gained by this work, it raises also the hope that it might lead to the development of new and more rational forms of treatment. Lindsay (1950) reported a method of treatment by injecting drugs into the frontal lobes of patients, and relevant in this connexion is some work of Tower's (1955), who has recently shown that certain epileptic patients have a biochemical brain lesion, which can be remedied by biochemical methods of treatment. It would seem that something might be gained from a wider collaboration between the physiologists, neurosurgeons and biochemists in studying the effects of intracranially administered drugs.

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